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Original Article

High visfatin expression predicts poor prognosis of upper tract urothelial carcinoma patients

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Abstract: Visfatin, a newly discovered adipocytokine, is a pro-inflammatory cytokine. This study aimed to evaluate the predictive value of visfatin on prognosis of patients with upper tract urothelial carcinoma. One-hundred and five patients (median age=64, range=24-84 years) were included in this study. Visfatin expression in upper tract urothelial carcinoma tissues was analyzed by immunohistochemistry. Visfatin expression was correlated with clinicopathologic variables using the χ^2 test. The prognostic value of visfatin for recurrence-free and cancer-specific survival was evaluated by Kaplan-Meier estimates, and the significance of differences between curves was evaluated by the log-rank test. Cox regression model was also used to evaluate the hazard ratios of visfatin on survival. High visfatin expression in upper tract urothelial carcinoma tissues was significantly correlated with tumor stage (P=0.001), grade (P=0.007) and p53 expression (P=0.07). High visfatin expression was associated with poor recurrence-free and cancer-specific survival. Cox regression analysis also revealed that visfatin is an independent predictor of recurrence-free (HR=3.22, P=0.009) and cancer-specific survival (HR=5.74, P=0.023). Our findings indicated that higher visfatin expression is a potential biomarker to predict patient survival. Further study is necessary to investigate the role of visfatin in the carcinogenesis of upper tract urothelial carcinoma.

Keywords: Nampt/PBEF/visfatin, upper tract urothelial carcinoma, immunohistochemistry, prognosis, survival

Introduction

Urothelial carcinoma (UC) is the most common malignancy in urinary tract. The incidence of renal pelvic and ureteral cancer is very rare, accounting for only 4% of all urothelial cancers [1]. In United States, renal pelvic cancer accounted for about only 8% of all renal cancers, and ureter cancer about 5% of all urothelial cancers. However, an unusually high incidence of upper tract urothelial carcinomas (UTUC) had been reported [2, 3], showing that there may be some unknown genetic and environment factors for UTUC in Taiwan.

Nephroureterectomy with excision of bladder cuff is the standard treatment for UTUC. Pathological characteristics, such as stage and grade, are the strongest factors to predict prognosis, but even with the same stage or grade, patients still may have different cancer behaviors. Our previous immunochemistry reports showed p53 [4], COX-2 [5], osteopontin [6], hypoxia-induced factor-1α [7], nuclear factor-κB [8] are the prognostic factors for UTUC. However, the exact molecular mechanisms of tumor invasion, recurrence and prognosis of this disease are not clear. Indeed, there is still no conclusive biomarker for cancer detection, prognosis prediction or treatment effect monitoring for UTUC.

Visfatin [pre-B-cell colony-enhancing factor (PBEF), nicotinamide mononucleotide adenylyltransferase (NAMPT)], a 52-kDa protein, is the

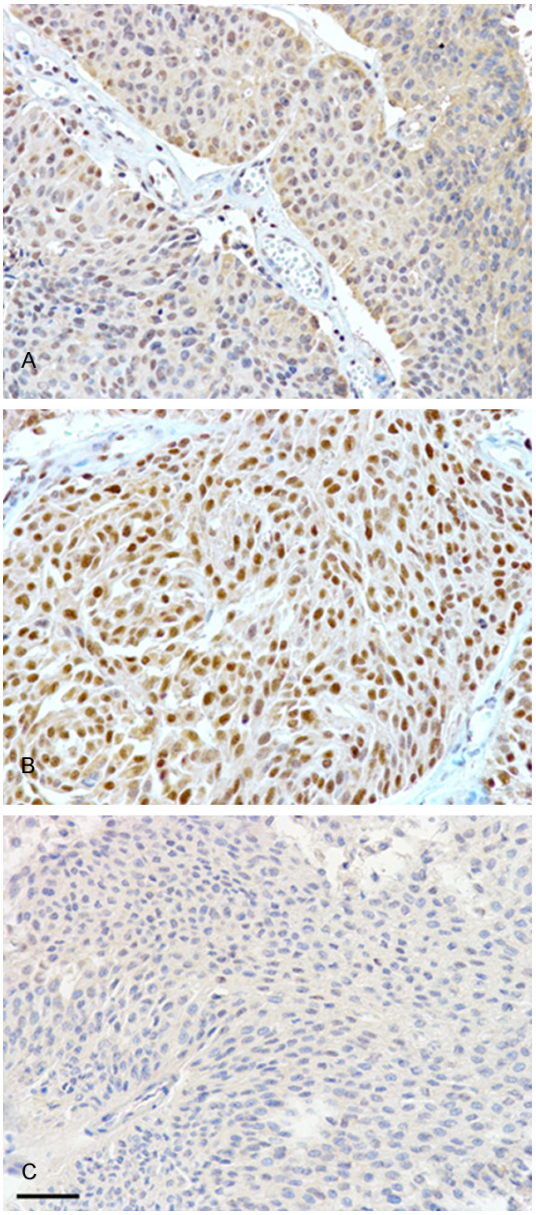

Figure 1. The expression of visfatin, as determined by immunohistochemistry, was divided into low (A) and high (B) nuclear staining of tumor cells in upper tract urothelial carcinomas. Negative control was showed in panel (C). (scale bar=50 μm).

rate-limiting enzyme of NAD biosynthesis from nicotinamide that regulates growth, apoptosis, DNA replication, repair and angiogenesis of mammalian cells [9, 10]. Cancer cells have a high rate of NAD^+ turnover compared to normal cells [11], and therefore, visfatin is essential for the survival of tumor cells. Accumulated evidences suggested that increased expression of visfatin is closely associated with the pathogenesis of colon [12], pancreas [13], gastric [14], prostate [15], malignant astrocytoma/glioblastoma [16] and breast cancers [17]. These reports indicate that visfatin can be considered a rational target in cancer. Consequently, several small molecule inhibitors of the enzyme are being investigated and developing [11, 18]. Recent evidence shown that pharmacological blockade of visfatin reduces viability in multiple types of cancer cells and can inhibit the growth of tumor xenografts *in vivo* [19, 20].

However, the expression of visfatin and its prognostic significance in UTUC is still unknown. In this study, we evaluated the expression levels of visfatin and P53 in tumor tissues and correlated them with clinicopathologic features in UTUC patients.

Materials and methods

Surgical specimens and clinicopathological data

One-hundred and five formalin-fixed UTUC samples were obtained from the Department of Urology, Kaohsiung Medical University Hospital from 1997-2006. The data were retracted from medical records retrospectively. All the patients received nephroureterectomy and excision of bladder cuff. The data were retracted from medical records retrospectively. Follow-Up protocol was decided according to NCCN guideline. Patients received cystoscopy by 3-month interval within 2 years after surgery and then increasing intervals thereafter. Bladder recurrence was defined as UC proved pathologically. Recurrence-free survival was defined as the time from the date of surgery to the date of bladder recurrence. This study protocol was reviewed and approved by the Institutional Review Board of Kaohsiung Medical University Hospital (KMUH-IRB-20120069).

Immunohistochemistry

Five-μm-thick sections from representative tissue blocks were cut, deparaffinized with xylene rinse, rehydrated with a graded alcohol series for 5 min each, and then rinsed with distilled water. Antigen retrieval was enhanced by autoclaving slides in sodium citrate buffer (10 mM, pH 6.0) for 30 min. Endogenous peroxidase activity was quenched by incubation in 3% hydrogen peroxide/methanol buffer for 10 min. The slides were incubated with a monoclonal

Table 1. Clinicopathological characteristics of patients with upper tract urothelial carcinoma and association with visfatin expression

		Visfatin		
		Low	High	
Variable[a]	Patient, no. (%)	n (%)	n (%)	*P*-Value[b]
No.	105 (100)	45 (42.9)	60 (57.1)	
Stage				
I/II	64 (61.0)	36 (80.0)	28 (46.7)	0.001
III/IV	41 (39.0)	9 (20.0)	32 (53.3)	
Grade				
Low	34 (32.4)	21 (46.7)	13 (21.7)	0.007
High	71(67.6)	24 (53.3)	47 (78.3)	
Gender				
Male	50 (47.6)	20 (44.4)	30 (50.0)	0.573
Female	55 (52.4)	25 (55.6)	30 (50.0)	
Age (years)				
<65	37 (35.2)	17 (37.8)	20 (33.3)	0.637
≥65	68 (64.8)	28 (62.2)	40 (66.7)	
BMI (kg/m^2)				
<25	67 (63.8)	27 (60.0)	40 (66.7)	0.482
≥25	38 (36.2)	18 (40.0)	20 (33.3)	
p53				
Low	37 (36.6)	23 (51.1)	14 (25.0)	0.007
High	64 (63.4)	22 (48.9)	42 (75.0)	

[a]Undetermined in small cases; [b]*P* by the chi-square test. BMI: body mass index.

antibody against visfatin (sc-166946, Santa Cruz Biotechnology, INC.) at a dilution of 1:500 overnight at 4°C in humidified chambers. The slides were washed three times in phosphate-buffered solution and further incubated with a biotinylated secondary antibody for 30 min at room temperature. Antigen-antibody complexes were detected by the avidin-biotin-peroxidase method using 3,3'-diaminobenzidine as a chromogenic substrate (Dako, Glostrup, Denmark). Finally, the slides were counterstained with hematoxylin and then examined by light microscopy.

Evaluation of immunohistochemical staining

Tumor immunostaining was examined by two qualified pathologists who were blinded to the patients' clinical status. Discrepancies in scoring between pathologists were reviewed jointly and a consensus was reached. Visfatin expression was determined by the percentage of positive stained cells. Specimen with stained cells less than 50% was marked as low visfatin expression, and those with stained cells more than 50% was marked as high visfatin expression.

Statistical analysis

All statistical analyses were performed using the SPSS 14.0 statistical package for PC (SPSS, Inc.). Chi-square test was applied to study the correlation of visfatin expression with tumor stage, tumor grade, gander, age at diagnosis, body mass index (BMI), tumor distant metastasis, hemodialysis, and serum creatinine level. Survival curves were generated using Kaplan-Meier estimates, and the significance of differences between curves was evaluated by the log-rank test. Furthermore, hazard ratios (HRs) and 95% confidence intervals (CIs) computed from univariate and multivariable Cox regression models were used for investigating the relationship between clinicopathological characteristics and survival. *P* values less than 0.05 were considered statistically significant.

Results

Figure 1 showed that low (A) and high (B) nuclear staining of tumor cells in UTUC. Negative control was showed in panel (C). (scale bar=50 μm).

The patients were regularly followed-up for median 45 months (ranged from 6 to 145 months). The demographic distribution of characteristics such stage, grade, gender, age, BMI, in 105 patients with UTUC recruited in this study are demonstrated in **Table 1**. As shown in **Table 1**, sixty (57.1%) cancer specimens expressed high visfatin staining. According to their visfatin expression status, there was a significant correlation in stage (P=0.001), grade (P=0.007) and p53 expression (P=0.007). But, visfatin expression status was not associated with gender, age, or BMI.

In **Table 2**, we showed the influence of clinicopathological parameters on UTUC tumor recurrence after surgery. We found that tumor grade and stage were significantly correlated with recurrence-free survival in univariate analysis. Visfatin expression was importantly correlated with UTUC recurrence (P<0.001). But, in multivariable analysis of recurrence-free survival of UTUC patients, only visfatin expression showed

Table 2. Univariate and multivariable analysis of recurrence-free survival for patients with upper tract urothelial carcinoma

Variable	Univariate			Multivariable		
	Hazard ratio	95% Confidence interval	*P*-Value	Hazard ratio	95% Confidence interval	*P*-Value
Stage						
III/IV	2.71	(1.40-5.25)	0.003	1.62	(0.80-3.25)	0.178
I/II	1.00			1.00		
Grade						
High	4.05	(1.68-9.76)	0.002	2.47	(0.99-6.12)	0.052
Low	1.00			1.00		
Gender						
Male	1.63	(0.85-3.11)	0.141	-	-	-
Female	1.00			-		
Age (years)						
≥65	0.85	(0.44-1.65)	0.637	-	-	-
<65	1.00			-		
BMI (kg/m^2)						
≥25	0.82	(0.42-1.61)	0.567	-	-	-
<25	1.00			-		
Visfatin						
High	4.70	(2.06-10.76)	<0.001	3.22	(1.34-7.76)	0.009
Low	1.00			1.00		

BMI: body mass index.

Table 3. Univariate and multivariable analysis of cancer-specific survival for patients with upper tract urothelial carcinoma

Variable	Univariate			Multivariable		
	Hazard ratio	95% Confidence interval	*P*-Value	Hazard ratio	95% Confidence interval	*P*-Value
Stage						
III/IV	6.80	(2.48-18.67)	<0.001	4.53	(1.58-12.95)	0.005
I/II	1.00			1.00		
Grade						
High	2.21	(0.81-5.99)	0.121	0.89	(0.31-2.55)	0.831
Low	1.00			1.00		
Gender						
Male	0.79	(0.34-1.86)	0.595	-	-	-
Female	1.00			-		
Age (years)						
≥65	0.75	(0.32-1.76)	0.502	-	-	-
<65	1.00			-		
BMI (kg/m^2)						
≥25	0.75	(0.30-1.84)	0.523	-	-	-
<25	1.00			-		
Visfatin						
High	9.04	(2.10-38.88)	0.003	5.74	(1.27-25.98)	0.023
Low	1.00			1.00		

BMI: body mass index.

it is an independent risk factor of cancer recurrence (P=0.009).

In **Table 3**, we examined the impact of clinicopathological parameters on UTUC patients' sur-

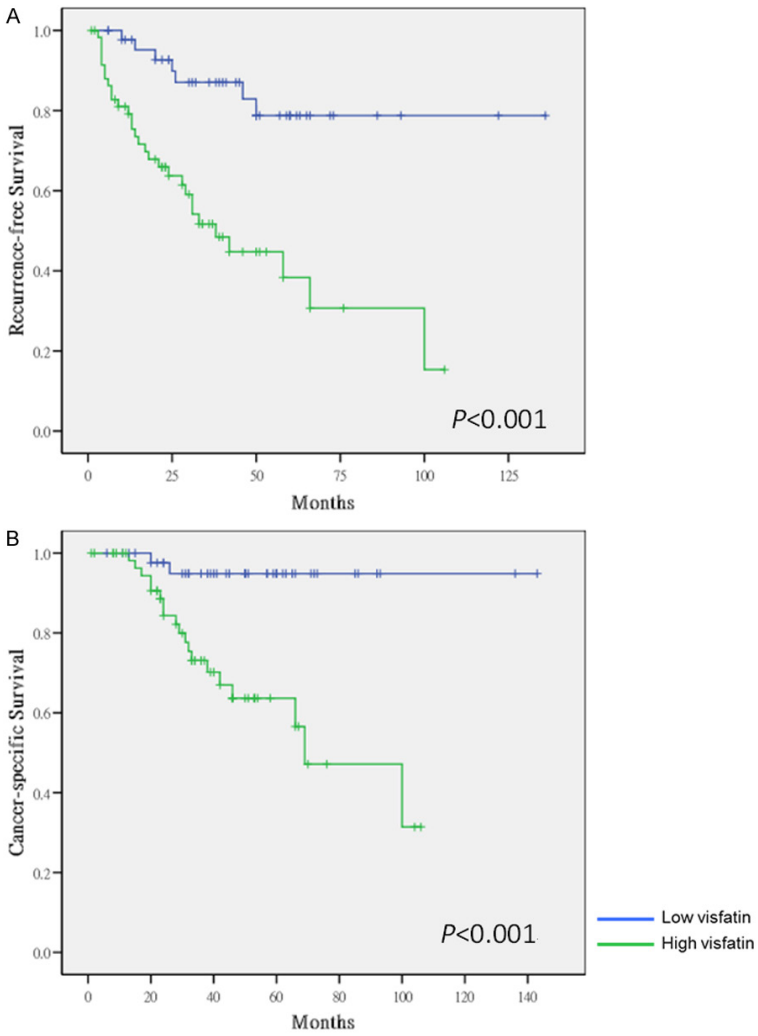

Figure 2. Kaplan-Meier survival curves for recurrence-free (A) and cancer-specific (B) survival of patients with low and high visfatin expression in upper tract urothelial carcinoma.

vival. We discovered that tumor stage and visfatin expression were both correlated significantly with worse cancer-specific survival in univariate and multivariable analysis.

Kaplan-Meier survival curves for recurrence-free (A) and cancer-specific (B) survival of patients with low and high visfatin expression in UTUC were indicated in **Figure 2**. **Figure 2A** showed high visfatin expression was a significant predictor for UTUC recurrence (P<0.001). **Figure 2B** showed high visfatin expression in UTUC predicted poor survival (P<0.001).

Discussion

Previous studies showed that high serum levels or tissue expression of visfatin were correlated with various cancers including breast cancer [21], colorectal cancer [22], prostate cancer [23], gastric cancer [14], endometrial cancer [24], melanoma [25], astrocytoma [16] and lymphomas [26]. In urothelial carcinoma, serum visfatin level was higher in patient with bladder cancer than in the control group. Besides, serum visfatin level predicted earlier recurrence in non-muscle invasive bladder cancer [27]. Another study suggested that visfatin is important in the pathogenesis of bladder cancer and its SNPs of visfatin gene might be a novel genetic biomarker for the prognosis of bladder cancer [28]. Accordingly, visfatin is thought to be a useful biomarker for tumorigenesis and for the prediction of cancer survival. But, there are no evidence that demonstrate the significant correlation between visfatin expression in tumor and clinico-pathological characteristics in urothelial carcinoma.

To the best of our knowledge, this is the first study to evaluate the prognostic significance of visfatin expression in UTUC. We found increased visfatin expression in UTUC correlated with advanced stages, higher tumor grade, and or higher p53 expression. We also demonstrated that the higher expression of visfatin in tumor tissues could predict poor prognosis of patients with UTUC.

Aside from the visfatin, we examined the p53 expression status in UTUC tissues. We found the positive correlation between visfatin and p53 expression. Corresponding to our previous work in UTUC, we had demonstrated that p53 was an independent predictor of poor progression-free (HR=3.74, P=0.025) and cancer-specific (HR=5.87, P=0.030) survival [13]. In bladder cancer molecular expression studies, most high grade invasive tumors had p53 mutation

[14]. Similar result had been illustrated by Reddy et al. who showed that visfatin overexpressed and its co-expression with p53 was associated with poor survival in glioblastoma [9]. Using HEK293T cells as a model, Thakur et al. reported that visfatin inhibition could elevate p53 activity and lead to carcinogenesis suppression. They concluded that apoptosis induced by visfatin inhibitors was associated with acetylation of p53, which is required for the functional activity of p53 [15].

In this study, we demonstrated that visfatin was identified as independent prognostic predictor for UTUC. Visfatin has recently gathered attention as an important role in carcinogenesis and a potential therapeutic target in cancer and other metabolic diseases [18]. In addition, the increased levels of visfatin observed in malignant versus benign tissues are associated with alterations in tumorigenic activity. There are several issues regarding the role of visfatin and its inhibitors as a therapeutic agent in control of human cancers. These inhibitors efficiently suppress NAD production in a time dependent manner and sustained reduction of NAD levels leads to loss of ATP and ultimately cell death [29]. Inhibition of visfatin activity using the specific inhibitors could be further evaluated for cancer treatment or as a sensitizer for chemotherapy [30].

Visfatin overexpression has been shown to promote acquired resistance to chemotherapeutic agents, including fluorouracil, doxorubicin, paclitaxel, etoposide, and phenylethyl isothiocyanate [15, 31]. Folgueira et al. also found visfatin expression in cancer tissue was higher in doxorubicin-resistant breast cancer [17]. In UTUC, the effect of cisplatin-based adjuvant chemotherapy after nephroureterectomy is still questionable [32]. Only part of the patients could have benefit from chemotherapy. Visfatin may play an important role to distinguish those who should receive chemotherapy from those who should not.

Limitations of this study were listed as following as: 1) we did not detect visfatin expression in serum of UTUC patients to demonstrate whether it can be used as a serological prognostic biomarker for UTUC patients; 2) we did not observe the differences of visfatin expression between normal urothelium and tumor tissue of UTUC patients. Thus, we cannot exam whether visfatin could be a risk factor of UTUC or not; 3) since this is a retrospective study, comprehensive data about the survival benefit of systemic chemotherapy cannot be collected thoroughly. We were unable to exam the effect of visfatin on survival of UTUC patients with chemotherapy.

In conclusion, we observed that visfatin expression in tumors was positively correlated with malignant behavior of UTUC. High visfatin expression predicted poor recurrence-free and cancer-specific survivals. Comprehensive studies are needed to clarify the detailed mechanisms of visfatin in UTUC development and progression.

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Disclosure of conflict of interest

None.

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