Original Article

Human U Three Protein 14a Expression is Increased in Hepatocellular Carcinoma and Associated with Poor Prognosis

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Abstract

Background: Human U three protein 14a (hUTP14a) promotes p53 degradation. Moreover, hUTP14a expression is upregulated in several types of tumors. However, the expression pattern of hUTP14a in hepatocellular carcinoma (HCC) remains unknown. The aim of this study was to investigate hUTP14a expression and its prognostic value in HCC.

Methods: The hUTP14a expression was evaluated using immunohistochemistry (IHC) in HCC tissue specimens. The correlations between hUTP14a expression and clinicopathological variables were analyzed. The Kaplan-Meier method was used to analyze the association between hUTP14a expression and survival. Independent prognostic factors associated with overall survival (OS) and disease-free survival (DFS) were analyzed using the Cox proportional-hazards regression model.

Results: The IHC data revealed that the hUTP14a positivity rate in HCC tissue specimens was significantly higher than that in nontumorous tissue specimens (89.9% vs. 72.7%, $P < 0.05$). The hUTP14a expression was detected in both the nucleolus and the cytoplasm. The positivity rate of nucleolar hUTP14a expression in HCC tissue specimens was higher than that in the nontumorous tissue specimens (29.3% vs. 10.1%, $P < 0.05$). No significant difference was found between HCC and nontumorous tissue specimens of cytoplasmic hUTP14a expression (60.6% vs. 62.6%, $P > 0.05$). In addition, no significant correlation was found between nucleolar hUTP14a expression and other clinicopathological variables. The 5-year OS and DFS rates in patients with positive nucleolar hUTP14a expression were significantly lower than those in patients with negative hUTP14a expression ($P = 0.004$ for OS, $P = 0.003$ for DFS). Multivariate analysis showed that nucleolar hUTP14a expression was an independent prognostic factor for OS ($P = 0.004$) and DFS ($P < 0.001$).

Conclusions: The positivity rate of hUTP14a expression was significantly higher in HCC specimens. Positive expression of nucleolar hUTP14a might act as a novel prognostic predictor for patients with HCC.

Key words: Hepatocellular Carcinoma; Human U Three Protein 14a; Poor Prognosis

Introduction

Liver cancer is the fifth most common malignancy and the third leading cause of cancer-related death globally.[1,2] It is estimated that approximately 782,500 new liver cancer cases and approximately 745,500 liver cancer-related deaths occur every year worldwide; approximately 50% of these deaths occur in China.[1] Hepatocellular carcinoma (HCC) constitutes approximately 70–90% of primary liver cancers. In China, the major underlying risk factors for HCC include chronic hepatitis B virus infection, aflatoxin B1 exposure, and alcohol abuse.[3-6] The prognosis of HCC is extremely poor, with a 5-year survival rate of 10–20%, because more than 70% of patients with HCC present with intrahepatic or extrahepatic metastasis at the time of the first diagnosis.[7] No more than 30% of patients with early stage HCC are suitable for curative treatments, including surgical resection, liver transplantation, and ablation.[8] However, more than 70% of

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patients experience recurrence even after curative therapy, despite improvements in treatments, such as transarterial chemoembolization (TACE) and targeted drugs.[9,10] The development of HCC is a complicated multistep process involving many molecules and signaling pathways. Despite the identification of many of these pivotal molecules,[11,12] the mechanism of HCC progression remains unclear. Therefore, it is of great importance to identify novel molecular factors involved in HCC progression to improve the prognostic prediction for patients with HCC.

Human U three protein 14a (hUTP14a) is a nucleolar protein, which plays an important role in 18S rRNA processing. Previous studies have found that hUTP14a is expressed in various kinds of tumor cells, and that it binds to p53 and promotes p53 protein degradation. Knockdown of hUTP14a in tumor cells results in cell growth arrest and apoptosis.[13] In addition, hUTP14a is not transcriptionally regulated by p53.[14] More importantly, high expression of hUTP14a has been found in tumor tissues, including colorectal cancer (CRC) and lung cancers (our unpublished data). These previous studies suggest that hUTP14a possesses oncogenic potential. However, the expression pattern and clinical significance of hUTP14a in HCC remain unknown.

Therefore, in this study, we used immunohistochemistry (IHC) to evaluate hUTP14a expression in human HCC tissue specimens and analyzed its correlations with the clinicopathological characteristics and prognosis of patients with HCC.

Methods

Patients and specimens

Formalin-fixed, paraffin-embedded blocks of HCC tissue and corresponding nontumorous liver tissues were collected from 99 patients with HCC who underwent curative hepatectomy between April 2010 and December 2011. The inclusion criterion was tumors pathologically confirmed as HCC. Exclusion criteria were (1) mixed HCC or cholangiocellular carcinoma, (2) emergence of extrahepatic metastasis, (3) no R0 resection, (4) existence of another type of primary tumor, and (5) ever received chemotherapy, radiation therapy, or TACE before the surgery. The patients included 82 men and 17 women, with a median age of 55 years (range, 32–81 years). The demographic, pathologic, and survival data of all patients were collected and analyzed, and the presence of HCC was pathologically confirmed. Detailed clinicopathological characteristics of patients are listed in Table 1. All human tissue specimens were collected using protocols approved by the Ethics Committee of the Peking University Health Science Center, and informed consent was obtained from all patients.

Immunohistochemistry and specimen evaluation

IHC was performed as previously described.[15] Briefly, the 4 μm-thick sections were dewaxed in xylene and gradually rehydrated. Endogenous peroxidases were blocked with 3% hydrogen peroxide. Antigen retrieval was performed by pressure cooking for 2 min in ethylenediaminetetraacetic acid at pH 9.0. After antigen retrieval, the sections were incubated with 10% goat serum for 30 min at room temperature. Subsequently, sections were incubated overnight with rabbit anti-hUTP14a polyclonal antibody (generated in our laboratory) at 4°C and were then incubated with horseradish peroxidase-conjugated goat anti-rabbit IgG (Zhongshan Golden Bridge Biotechnology, Beijing, China) at 37°C for 30 min. Immunocomplexes were visualized using 3,3'-diaminobenzidine (Dako, Carpinteria, CA, USA). Slides were counterstained with light hematoxylin, dehydrated, and cover-slipped.

Table 1: Positivity rates of hUTP14a expression in hepatocellular carcinoma tissue specimens and nontumorous tissue specimens, *n* (%)

Tumor tissue specimens	Nontumorous tissue specimens		Total	χ^2	*P*
	Negative	Positive			
Negative	9 (9.1)	1 (1.0)	10 (10.1)	22.066	<0.05
Positive	18 (18.2)	71 (71.7)	89 (89.9)		
Total	27 (27.3)	72 (72.7)	99 (100)		

hUTP14a: Human U three protein 14a.

The histological slides were evaluated by two independent observers blinded to all clinical, pathological, and outcome information, including an experienced pathologist. Any score discrepancy was resolved by discussion to reach a consensus. The specimens were categorized into four groups on the basis of IHC results: negative (−), 0–10% positive cells; faintly positive (+), 10–25% positive cells; moderately positive (++), 25–50% positive cells; and highly positive (+++), and ≥50% positive cells.

Follow-up

All 99 patients were followed up after hepatic resection. The median duration of follow-up was 55 months (range, 2–75 months). Patient follow-up data were collected from the patients' medical records at Beijing Cancer Hospital. A telephonic follow-up was conducted every 3 months until death. During follow-up, tumors recurred in 52 patients (52.5%). Forty-one patients (41.4%) died of disease-related causes by the end of the follow-up period.

Statistical analysis

All statistical analyses were carried out using SPSS software 17.0 version (SPSS Inc., Chicago, IL, USA) and GraphPad Prism Software (GraphPad Software, San Diego, CA, USA). The hUTP14a expression in the HCC tissue specimens was compared with that in nontumorous liver tissue specimens using the McNemar's test. Associations between hUTP14a IHC staining and clinicopathological variables were analyzed using the Pearson's Chi-square test. Patient survival analysis was evaluated using the Kaplan-Meier method, and the difference between the survival curves of nucleolar hUTP14a positive and negative groups for overall survival (OS), i.e., the period from hepatic resection to death

or the last time of follow-up, and disease-free survival (DFS), i.e., the period from hepatic resection to recurrence or death or the last time of follow-up, was analyzed using the log-rank test. Univariate and multivariate survival analyses were performed using the Cox proportional hazard model. A value of $P < 0.05$ was considered statistically significant.

Results

Positivity rate of human U three protein 14a expression in human hepatocellular carcinoma tissue specimens

To explore the potential role of hUTP14a in HCC, we used IHC to evaluate hUTP14a expression in HCC tissue specimens and the corresponding nontumorous tissue specimens. As shown in Figure 1, hUTP14a expression was detected in the nucleolus and cytoplasm of HCC cells. The hUTP14a expression was detected in 89 out of the 99 (89.9%) of HCC tissue specimens, whereas it was detected in 72 (72.7%) of the corresponding nontumorous tissue specimens. Thus, the positivity rate of hUTP14a expression in HCC tissue specimens was significantly higher than that in the nontumorous tissue specimens (89.9% vs. 72.7%, $P < 0.05$) [Table 1]. Specifically, nucleolar and cytoplasmic hUTP14a expression was detected in 29 (29/99, 29.3%) and 60 (60/99, 60.6%) HCC tissue specimens, respectively. In comparison, nucleolar and cytoplasmic hUTP14a expression was detected in 10 (10/99, 10.1%) and 62 (62/99, 62.6%) corresponding nontumorous tissue specimens, respectively. Only the positivity rate of nucleolar hUTP14a expression in HCC tissue specimens was significantly higher than that in the nontumorous tissue specimens (29.3% vs. 10.1%, respectively; $P < 0.05$) [Table 2]. However, as shown in Table 3, no significant difference was found between the positivity rates for cytoplasmic hUTP14a expression in the HCC and nontumorous tissue specimens (60.6% vs. 62.6%, $P > 0.05$).

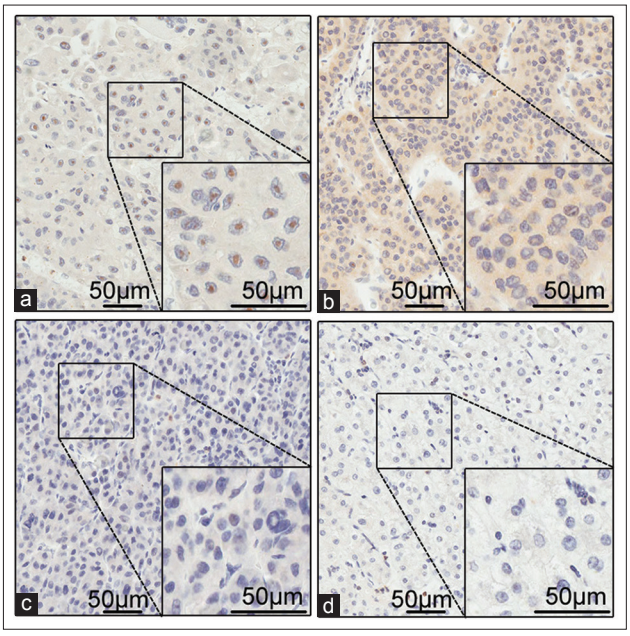

Figure 1: Immunohistochemical analysis of hUTP14a in hepatocellular carcinoma and corresponding nontumorous liver tissue specimens. Representative immunohistochemical staining of hUTP14a in hepatocellular carcinoma tissue specimens (a, nucleolar positive staining; b, cytoplasmic positive staining; c, negative staining) and adjacent nontumorous liver tissue specimens (d, negative staining), $n = 99$, scale bars represent 50 μm. hUTP14a: Human U three protein 14a.

Associations between human U three protein 14a expression and clinicopathological characteristics of hepatocellular carcinoma

Given that the nucleolar hUTP14a expression was significantly upregulated in HCC tissue specimens, the relationship between nucleolar hUTP14a expression and the clinicopathological characteristics of HCC was analyzed. As shown in Table 4, nucleolar hUTP14a expression was not correlated with any clinicopathological characteristic ($P > 0.05$).

Association between nucleolar human U three protein 14a expression in hepatocellular carcinoma tissue specimens and patient survival

A total of 70 patients were negative and 29 patients were positive for nucleolar hUTP14a staining of HCC specimens. The median follow-up duration was 32 months (range 4–72 months) for the nucleolar hUTP14a-positive group and 60 months (range 2–75 months) for the nucleolar hUTP14a-negative group. The patients' Kaplan-Meier survival curves are shown in Figure 2. The 5-year OS rates in the nucleolar hUTP14a-negative and -positive groups were 69.6% and 44.8%, respectively [$P = 0.004$; Figure 2a]. The 5-year DFS rates in the nucleolar hUTP14a-negative and -positive groups were 56.7% and 27.2%, respectively [$P = 0.003$; Figure 2b]. These results

Table 2: Positivity rates of nucleolar hUTP14a expression in hepatocellular carcinoma tissue specimens and nontumorous tissue specimens, $n = 99$, n (%)

Tumor tissue specimens	Nontumorous tissue specimens		Total	χ^2	P
	Negative	Positive			
Negative	60 (60.6)	10 (10.1)	70 (70.7)	4.608	<0.05
Positive	29 (29.3)	0	29 (29.3)		
Total	89 (89.9)	10 (10.1)	99 (100)		

hUTP14a: Human U three protein 14a.

Table 3: Positivity rates of cytoplasmic hUTP14a expression in hepatocellular carcinoma tissue specimens and nontumorous tissue specimens, $n = 99$, n (%)

Tumor tissue specimens	Nontumorous tissue specimens		Total	χ^2	P
	Negative	Positive			
Negative	19 (19.2)	20 (20.2)	39 (39.4)	3.538	>0.05
Positive	18 (18.2)	42 (42.4)	60 (60.6)		
Total	37 (37.4)	62 (62.6)	99 (100)		

hUTP14a: Human U three protein 14a.

Table 4: Relationship between positivity rate of nucleolar hUTP14a expression and clinicopathological variables of patients with hepatocellular carcinoma, *n* = 99, *n* (%)

Variables	Number of specimens	Nucleolar hUTP14a		χ^2	*P*
		Negative	Positive		
Tumor size					
≤5 cm	58 (58.6)	43 (61.4)	15 (51.7)	0.796	0.372
>5 cm	41 (41.4)	27 (3.6)	14 (48.3)		
Serum AFP level					
≤200 ng/ml	53 (53.5)	36 (51.4)	17 (58.6)	0.426	0.514
>200 ng/ml	46 (46.5)	34 (48.6)	12 (41.4)		
Tumor nodule number					
Solitary	79 (79.8)	54 (77.1)	25 (86.2)	1.045	0.307
Multiple	20 (20.2)	16 (22.9)	4 (13.8)		
Microscopic vascular invasion					
Absent	67 (67.7)	45 (64.3)	22 (75.9)	1.256	0.262
Present	32 (32.3)	25 (35.7)	7 (24.1)		
Hepatic cirrhosis					
Absent	17 (17.2)	9 (12.9)	8 (27.6)	3.128	0.077
Present	82 (82.8)	61 (87.1)	21 (72.4)		
Edmondson–Steiner grade					
1, 2	77 (77.8)	58 (82.9)	19 (65.5)	3.567	0.059
3, 4	22 (22.2)	12 (17.1)	10 (34.5)		
HBV infection					
Absent	20 (20.2)	12 (17.1)	8 (27.6)	1.387	0.239
Present	79 (79.8)	58 (82.9)	21 (72.4)		
Distant metastasis					
Absent	94 (94.9)	67 (95.7)	27 (93.1)	0.291	0.589
Present	5 (5.1)	3 (4.3)	2 (6.9)		

All data are presented as number of specimens (%). *P* values were calculated in SPSS 17.0 using a Chi-square test. $P<0.05$ was considered statistically significant. AFP: Alpha-fetoprotein; HBV: Hepatitis B virus; hUTP14a: Human U three protein 14a.

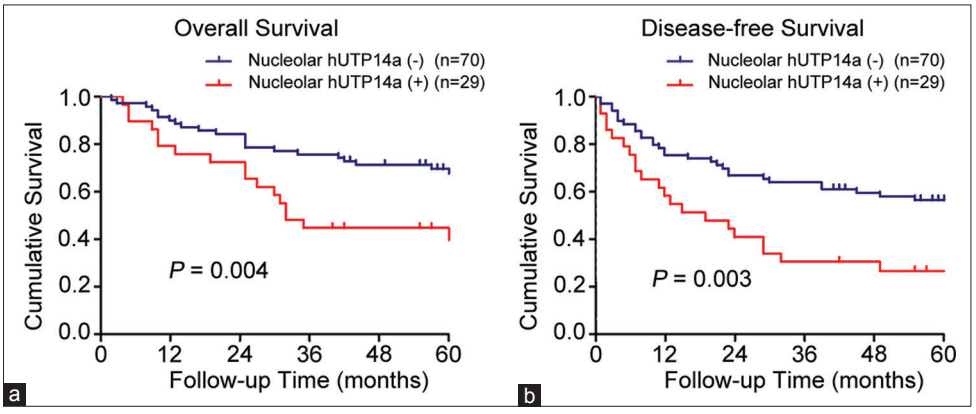

Figure 2: Kaplan-Meier curves of OS and DFS according to nucleolar hUTP14a expression in patients with hepatocellular carcinoma. Kaplan-Meier analysis of OS (a) and DFS (b) of 99 patients with hepatocellular carcinoma according to the positivity rate of nucleolar hUTP14a expression in tumor tissue specimens. $P = 0.004$ for OS and $P = 0.003$ for DFS, log-rank test. OS: Overall survival; DFS: Disease-free survival; hUTP14a: Human U three protein 14a.

indicated that positive nucleolar hUTP14a expression correlated with poor survival of HCC patients.

The human U three protein 14a expression as an independent prognostic factor in hepatocellular carcinoma

Furthermore, univariate and multivariate Cox regression analyses were performed to identify independent prognostic factors affecting the survival of patients with HCC after curative liver resection. Univariate Cox regression analysis revealed that tumor size >5 cm (hazard ratio [*HR*], 2.9; 95% confidence interval [*CI*], 1.5–5.4; $P = 0.001$), serum alpha-fetoprotein (AFP) level >200 ng/ml (*HR*, 1.9; 95% *CI*, 1.0–3.5; $P = 0.041$), microscopic vascular invasion (*HR*, 2.4; 95% *CI*, 1.3–4.5; $P = 0.005$), Edmondson-Steiner Grade 3 or 4 (*HR*, 2.1; 95% *CI*, 1.1–4.1; $P = 0.027$), and positive nucleolar hUTP14a expression (*HR*, 2.4; 95% *CI*, 1.3–4.5; $P = 0.005$) were associated with poor OS [Table 5].

Multivariate Cox regression analysis showed that in addition to tumor size >5 cm (*HR*, 2.5; 95% *CI*, 1.3–5.0; *P* = 0.006), serum AFP level >200 ng/ml (*HR*, 2.0; 95% *CI*, 1.0–3.7; *P* = 0.038), microscopic vascular invasion (*HR*, 2.1; 95% *CI*, 1.1–4.2; *P* = 0.029), and positive nucleolar hUTP14a expression (*HR*, 2.7; 95% *CI*, 1.4–5.2; *P* = 0.004) were correlated with poor prognosis of patients with HCC [Table 5].

Similarly, univariate analysis indicated that tumor size >5 cm (*HR*, 2.7; 95% *CI*, 1.5–4.6; *P* < 0.001), serum AFP level >200 ng/ml (*HR*, 1.7; 95% *CI*, 1.0–3.0; *P* = 0.049), microscopic vascular invasion (*HR*, 3.4; 95% *CI*, 2.0–5.9; *P* < 0.001), Edmondson-Steiner Grade 3 or 4 (*HR*, 1.9; 95% *CI*, 1.0–3.5; *P* = 0.038), and positive nucleolar hUTP14a expression (*HR*, 2.3; 95% *CI*, 1.3–4.0; *P* = 0.004) were correlated with DFS. Multivariate Cox regression analysis showed that tumor size >5 cm (*HR*, 2.2; 95% *CI*, 1.2–3.9; *P* = 0.010), serum AFP level >200 ng/ml (*HR*, 1.8; 95% *CI*, 1.0–3.1; *P* = 0.049), microscopic vascular invasion (*HR*, 3.4; 95% *CI*, 1.8–6.2; *P* < 0.001), Edmondson-Steiner Grade 3 or 4 (*HR*, 1.9; 95% *CI*, 1.9–3.6; *P* = 0.040), and positive hUTP14a expression (*HR*, 2.9; 95% *CI*, 1.6–5.3; *P* < 0.001) were independent risk factors for poor DFS [Table 6].

Table 5: Univariable and multivariable Cox regression analysis of prognostic factors of overall survival in patients with hepatocellular carcinoma

Variables	Univariate analysis		Multivariate analysis	
	HR (95% *CI*)	*P*	*HR* (95% *CI*)	*P*
Tumor size (cm)				
≤5	1	0.001	1	0.006
>5	2.9 (1.5–5.4)		2.5 (1.3–5.0)	
Serum AFP level (ng/ml)				
≤200	1	0.041	1	0.038
>200	1.9 (1.0–3.5)		2.0 (1.0–3.7)	
Tumor nodule number				
Solitary	1	0.064		
Multiple	1.9 (1.0–3.7)			
Microscopic vascular invasion				
Absent	1	0.005	1	0.029
Present	2.4 (1.3–4.5)		2.1 (1.1–4.2)	
Hepatic cirrhosis				
Absent	1	0.268		
Present	0.6 (0.2–1.5)			
Edmondson–Steiner Grade				
1, 2	1	0.027	1	0.053
3, 4	2.1 (1.1–4.1)		2.0 (1.0–4.0)	
HBV infection				
Absent	1	0.398		
Present	1.4 (0.7–2.8)			
Nucleolar hUTP14a				
Negative	1	0.005	1	0.004
Positive	2.4 (1.3–4.5)		2.7 (1.4–5.2)	

*HR*s and 95% *CI*s were calculated using univariate or multivariate Cox proportional hazards regression in SPSS 17.0. *P* values were calculated using univariate or multivariate Cox proportional hazards regression in SPSS 17.0. *P*<0.05 was considered statistically significant. AFP: Alpha-fetoprotein; HBV: Hepatitis B virus; *HR*s: Hazard ratios; *CI*: Confidence interval; hUTP14a: Human U three protein 14a.

Discussion

HCC is one of the most common malignancies worldwide. In many countries, especially in China, the prognosis of HCC remains unsatisfactory despite the significant improvements in surgical techniques and perioperative therapies.[16,17] Thus, novel clinicopathological or molecular prognostic factors are needed to predict tumor biology and identify patients with higher risk of metastasis or recurrence. hUTP14a, a nucleolar protein involved in 18S rRNA processing, was originally identified as a 1A6/DRIM-interacting protein by a yeast two-hybrid method. A previous study showed that ectopic expression of hUTP14a caused p53 protein degradation, and that knockdown of hUTP14a led to cell cycle arrest and apoptosis.[13] In addition, hUTP14a is upregulated in several types of human cancer tissues. However, little is known about the expression pattern and potential role of hUTP14a in HCC tissues. In the present study, we first showed that hUTP14a was upregulated in HCC tissues and demonstrated that nucleolar hUTP14a is an independent prognostic factor for poor survival in patients with HCC.

Recently, nucleolar proteins have been shown to play critical roles in carcinogenesis and prognosis of human cancers. Nucleolar proteins participate in tumor progression not only by promoting ribosome biogenesis but also by maintaining genome stability, regulating cell cycle progression, and regulating cellular senescence.[18] For example, nucleolar protein PES1, which is associated with neuroblastoma differentiation, has been shown to be an indicator of poor prognosis in patients with neuroblastoma. PES1 functions not only in ribosome genesis but also in DNA damage, apoptosis, and differentiation.[19] A previous report revealed that hUTP14a participates in 18S rRNA processing and promotes p53 degradation. Functionally, knockdown of hUTP14a inhibited cell growth by arresting cells in G1 phase and increasing cell apoptosis.[13] In the present study, we found that hUTP14a is another nucleolar protein that is upregulated in HCC and is an independent prognostic factor for poor survival of patients with HCC. Thus, our study elucidates the critical role of nucleolar proteins in HCC.

In the present study, we found that hUTP14a was expressed not only in the nucleolus but also in the cytoplasm; however, only nucleolar hUTP14a was significantly upregulated in HCC tissue specimens. This result is not surprising because many nucleolar proteins have different cellular localizations in human cancers. The same protein expressed at different cellular locations might perform different functions and indicate different tumor behaviors. For instance, protein

Table 6: Univariable and multivariable Cox regression analysis of prognostic factors of disease-free survival in patients with hepatocellular carcinoma

Variables	Univariate analysis		Multivariate analysis	
	HR (95% *CI*)	*P*	*HR* (95% *CI*)	*P*
Tumor size (cm)				
≤5	1	<0.001	1	0.010
>5	2.7 (1.5–4.6)		2.2 (1.2–3.9)	
Serum AFP level (ng/ml)				
≤200	1	0.049	1	0.049
>200	1.7 (1.0–3.0)		1.8 (1.0–3.1)	
Tumor nodule number				
Solitary	1	0.113		
Multiple	1.6 (0.9–3.0)			
Microscopic vascular invasion				
Absent	1	<0.001	1	<0.001
Present	3.4 (2.0–5.9)		3.4 (1.8–6.2)	
Hepatic cirrhosis				
Absent	1	0.273		
Present	0.6 (0.3–1.4)			
Edmondson–Steiner Grade				
1, 2	1	0.038	1	0.040
3, 4	1.9 (1.0–3.5)		1.9 (1.0–3.6)	
HBV infection				
Absent	1	0.781		
Present	1.0 (0.6–2.1)			
Nucleolar hUTP14a				
Negative	1	0.004	1	<0.001
Positive	2.3 (1.3–4.0)		2.9 (1.6–5.3)	

*HR*s and 95% *CI*s were calculated using univariate or multivariate Cox proportional hazards regression in SPSS 17.0. *P* values were calculated using univariate or multivariate Cox proportional hazards regression in SPSS 17.0. $P<0.05$ was considered statistically significant. AFP: Alpha-fetoprotein; HBV: Hepatitis B virus; *HR*s: Hazard ratios; *CI*s: Confidence intervals; hUTP14a: Human U three protein 14a.

N-acetyltransferase 10 (NAT10), a nucleolar protein involved in many cellular processes such as histone acetylation and DNA damage response, showed nucleolar, nucleoplasmic, cytoplasmic, and plasma membrane localization in CRC.[20,21] Zhang *et al*.[21] showed that this redistribution of NAT10 might be a result of increased stability and nuclear export; furthermore, NAT10 expression in the plasma membrane was associated with aggressive clinical behavior in CRC. In addition, Liu *et al*.[22] suggested that NAT10 is a crucial regulator of p53 homeostasis, NAT10 stabilizes p53 by counteracting the activity of Mdm2; moreover, in response to DNA damage, nucleolar NAT10 translocates to the nucleoplasm and activates p53 to protect cells. These findings indicate that the expression of NAT10 at different cellular locations can have opposite effects. A previous study showed that hUTP14a caused p53 protein degradation, indicating its oncogenic potential.[13] In the present study, we found a significant difference in the expression of nucleolar hUTP14a between HCC and nontumorous tissue specimens. In addition, positive nucleolar hUTP14a indicated poor survival in patients with HCC, which is consistent with the oncogenic activity of hUTP14a. However, the expression of cytoplasmic hUTP14a did not differ between HCC and nontumorous tissue specimens. Therefore, cytoplasmic hUTP14a cannot serve as an indicator of prognosis in patients with HCC. We hypothesize that hUTP14a translocates from the cytoplasm to the nucleolus in a manner similar to NAT10, and that this translocation increases its oncogenic activity. Further studies are needed to investigate the mechanism and effect of hUTP14a translocation in tumor cells.

Multivariable Cox regression analysis showed that nucleolar hUTP14a is an independent prognostic factor in patients with HCC. In addition, as previously reported, tumor size, serum AFP level, and microscopic vascular invasion were confirmed as negative factors for survival. A large body of evidence has confirmed that a large tumor size is an unfavorable prognostic factor in patients with HCC, especially in patients with surgically resected solitary HCC.[23,24] In addition, serum AFP level is still regarded as one of the most important prognostic markers for patients with HCC. Detection of serum AFP levels is a relatively well-established method that is used routinely for identifying HCC patients with a high risk of recurrence and metastasis after curative resection.[25] Microscopic vascular invasion occurs in approximately 44% of patients with HCC at the time of death.[26] Furthermore, the presence of microscopic vascular invasion has an adverse effect on prognosis. It is reported that the median survival time of patients who have unresectable HCC without microscopic vascular invasion is 10–24 months; however, the median survival time decreases significantly to 2–4 months if microscopic vascular invasion is present.[27] The present study results provide a new prognostic factor for HCC. Since nucleolar hUTP14a expression is associated with a high incidence of tumor recurrence and poor survival, more careful and strict surveillance of patients with this expression pattern might be indispensable after curative treatment. Adjuvant therapy might also be useful for preventing tumor recurrence and enhancing the efficacy of surgery in patients with nucleolar hUTP14a expression. The monitoring of such prognostic factors will help screen patients with poor prognosis more accurately and will complement the currently known prognostic indicators. It should be noted that the clinical sample size in the present study was relatively small. Therefore, further studies with larger sample sizes are required to reduce potential selection bias. In our study, nucleolar hUTP14a expression was not related to any clinicopathological variable. However, it was related with poor survival. One possible reason for this discrepancy is that some clinicopathological variable that was not included in this study might have differed between patients with and without nucleolar hUTP14a expression and have affected patient survival.

In summary, this study revealed that nucleolar hUTP14a is a novel independent prognostic factor in HCC. Thus,

hUTP14a might be a promising prognostic tool and potential therapeutic target in patients with HCC. Further studies on other types of tumors are required for a comprehensive understanding of the role of hUTP14a in human cancers.

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Conflicts of interest

There are no conflicts of interest.

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