Prognostic value of *ATAD3* gene cluster expression in hepatocellular carcinoma

XIAOLING LIU[1*], GANG LI[2*], LIANG AI[2], QIUWEN YE[2], TINGDONG YU[3] and BURONG YANG[2]

[1]Department of Geriatrics, The First Affiliated Hospital of Kunming Medical University, Kunming, Yunnan 650032; [2]Department of Abdominal Surgery, The Third Affiliated Hospital of Kunming Medical University, Kunming, Yunnan 650118; [3]Department of Hepatobiliary Surgery, The First Affiliated Hospital of Guangxi Medical University, Nanning, Guangxi 530021, P.R. China

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Abstract. ATPase family AAA domain-containing protein 3 (*ATAD3*) is a mitochondrial membrane-bound ATPase that is involved in a number of cellular processes and is linked with the progression of various types of malignancies. In primates, the *ATAD3* gene cluster contains *ATAD3A*, *ATAD3B* and *ATAD3C*. The association between *ATAD3* gene cluster expression and hepatocellular carcinoma (HCC) remains unknown. Therefore, the present study examined the prognostic significance of *ATAD3* gene cluster expression in patients with HCC. Box plots of expression differences between HCC and normal liver tissues for the *ATAD3* family genes were obtained from the online tool Gene Expression Profiling Interactive Analysis. Data from 360 patients with HCC in The Cancer Genome Atlas database were analyzed. Kaplan-Meier analysis and a Cox regression model were used to calculate median survival time (MST) and overall survival (OS). *ATAD3A* and *ATAD3B* expression levels were higher in HCC compared with normal liver tissues (P<0.05). However, *ATAD3C* expression was significantly decreased in HCC tissues compared with normal liver tissues (P<0.05). *ATAD3A* [P=0.017, hazard ratio (HR)=1.54, 95% confidence interval (CI)=1.08-2.20; adjusted P=0.032; adjusted HR=1.52; 95% CI=1.04-2.22] and *ATAD3B* (P=0.026, HR=1.49, 95% CI=1.05-2.13; adjusted P=0.031, adjusted HR=1.52, 95% CI=1.04-2.21) expression levels were significantly associated with OS. A joint-effects analysis revealed that patients with high *ATAD3A* and *ATAD3B* expression had reduced OS rates compared with patients with low *ATAD3A* and *ATAD3B* expression (P=0.007, HR=1.77, 95% CI=1.16-2.69; adjusted P=0.013, adjusted HR=1.76, 95% CI=1.13-2.75). In conclusion, *ATAD3A* and *ATAD3B* may serve as potential prognostic biomarkers for patients with HCC.

Correspondence to: Dr Burong Yang, Department of Abdominal Surgery, The Third Affiliated Hospital of Kunming Medical University, 519 Kunzhou Road, Kunming, Yunnan 650118, P.R. China
E-mail: yangburong@163.com

*Contributed equally

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Introduction

Liver cancer is one of the most prevalent types of malignancy worldwide as the annual estimated rate reached 782,500 novel cases and ~745,500 liver cancer-associated mortalities in 2012 (1). In China, patients account for ~50% of all these cases and mortalities (1). Hepatocellular carcinoma (HCC) is the major histologic liver cancer subtype, representing 80% of all liver malignancies (2). Although surgical resection and liver transplantation are used in the treatment of early-stage HCC, the overall prognosis remains poor, due to high recurrence rates (3). A number of studies have reported that gene expression signatures are associated with the prognosis of HCC (4-6). Therefore, identifying novel biomarkers that predict prognosis and may guide individualized treatment for HCC would greatly benefit patients.

ATPase family AAA domain-containing protein 3 (*ATAD3*) is a mitochondrial membrane-bound ATPase that was first identified as a component of the mouse liver inner mitochondrial membrane using a proteomic approach (7) and was subsequently discovered to be overexpressed in head and neck carcinomas (8). Subsequent studies have reported that ATAD3 serves important roles in *Caenorhabditis elegans* and *Drosophila melanogaster* development, indicating that *ATAD3* is associated with proliferation and differentiation (9,10). In primates, the *ATAD3* gene cluster contains *ATAD3A*, *ATAD3B* and *ATAD3C*. *ATAD3A* is the ancestral form of *ATAD3*, while *ATAD3B* and *ATAD3C* are similar, however, they contain important mutated residues (11). These three genes are located side-by-side at the end of chromosome 1 (locus 1p36.33).

ATAD3 is a member of the family of AAA-ATPases, which are involved in a number of cellular processes, including transcription, replication, translation, proteolysis, and vesicular transport (12). In HeLa cells, *ATAD3* was reported in a large multi-molecular complex associated with mitochondrial DNA (mtDNA) that serves a role in mtDNA replication and transcription (13). *ATAD3* protein has displacement loop binding activity, which allows it to form or segregate mitochondrial

nucleoids (14). However, Bogenhagen *et al* (15) have reported that *ATAD3A* and *ATAD3B* indirectly interact with mtDNA, mediated by topology rather than the C-terminal AAA domain. Therefore, they do not have the opportunity to bind to mtDNA D-loops. Subsequent results have demonstrated that ATAD3A controls mitochondrial dynamics between the outer and inner membranes, and that the N-terminal region of ATAD3A is outside the inner membrane, while the C-terminal region is within the matrix (16,17). *ATAD3* deficiency is associated with aberrant mtDNA organization and cholesterol metabolism in the central nervous system (18).

ATAD3 expression was originally reported to produce autoimmune responses in patients with lung adenocarcinoma or uterine cervical cancer (19,20) and to be associated with tumorigenesis (11). Studies have reported that *ATAD3* expression is linked with the progression of head and neck cancers (8), non-Hodgkin's lymphoma (21), lung cancer (22), uterine cervical cancer (23), prostate cancer (24), and glioma (25). However, to the best of our knowledge, there have been no studies investigating associations between *ATAD3* expression and HCC. In the present study, the prognostic value of *ATAD3* gene cluster expression was investigated in HCC to determine it potential as a biomarker for this disease.

Materials and methods

ATAD3 gene cluster expression in HCC and normal liver tissues. Box plots comparing expression levels of the *ATAD3* gene cluster in HCC (n=369) vs. normal liver tissues (n=50) were downloaded from the online tool Gene Expression Profiling Interactive Analysis (http://gepia.cancer-pku.cn/), which uses data derived from The Cancer Genome Atlas (TCGA; http://tcga-data.nci.nih.gov/tcga). Significance cut-off level was set at P=0.05.

Patient information. Clinical data and *ATAD3A*, *ATAD3B* and *ATAD3C* mRNA levels of the 360 patients were obtained from the online websites OncoLnc (http://www.oncolnc.org/) and TCGA. The present study's results are partially based on data generated by TCGA Research (http://cancergenome.nih.gov/). The included clinical data were race, sex, age, body mass index (BMI), tumor node metastasis (TNM) stage (the seventh AJCC staging system) (26), survival time (days), and survival status.

Survival analysis. *ATAD3A*, *ATAD3B* and *ATAD3C* mRNA expression levels from TCGA were individually divided into two groups by their 50% cut-off values, resulting into the high-expression (n=180) and low-expression groups (n=180). Overall survival (OS) was analyzed by the Cox proportional hazards regression model adjusted by sex, age, and tumor stage.

Joint-effects analysis. *ATAD3A* and *ATAD3B* expression indicated statistically significant associations with OS in the patient cohort with HCC. Therefore, a joint-effects analysis of the combination of *ATAD3A* and *ATAD3B* with group I (low *ATAD3A* and *ATAD3B* expression), group II (low *ATAD3A* and high *ATAD3B* expression), group III (high *ATAD3A* and low *ATAD3B* expression), and group IV (high *ATAD3A* and *ATAD3B* expression) was performed. Sex, age, and tumor stage were adjusted in the Cox proportional hazards regression model.

Gene co-expression network analysis. In order to predict gene function and to construct a pathway for the *ATAD3* genes, the Database for Annotation, Visualization and Integrated Discovery (DAVID; https://david.ncifcrf.gov/content.jsp?file=citation.htm) was used to carry out the enriched Gene Ontology (GO) terms and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathways (27). Cytoscape 3.6.0 software (https://cytoscape.org/) was used to construct biological networks (28).

Statistical analysis. Median survival time (MST) and OS were calculated using the Kaplan-Meier method with log-rank tests. The Cox proportional hazards regression model was used to perform univariate and multivariate survival analyses. Hazard ratios (HR) and 95% confidence intervals (CI) were calculated subsequent to adjusting for sex, age, and tumor stage. All statistical analyses were performed with SPSS version 22.0 (IBM Corp., Armonk, NY, USA), with P-values <0.05 considered to indicate a statistically significant difference.

Results

Analysis of ATAD3 gene cluster expression in HCC and normal liver tissues. Expression data from 369 HCC and 50 normal liver samples were analyzed by box plots, and the results indicated that *ATAD3A* and *ATAD3B* were significantly overexpressed in HCC tissues compared with normal liver tissues (P<0.05; Fig. 1). However, the expression level of *ATAD3C* was significantly reduced in HCC tissues compared with normal liver tissues (P<0.05; Fig. 1).

TCGA database patient characteristics. Clinical characteristics of the 360 patients from the TCGA database are presented in Table I. The cohort included 244 male and 116 female patients, and the median age was 61 years. The analysis indicated that TNM stage was significantly associated with OS (P<0.001; HR=2.50; 95% CI=1.72-3.63), whereas neither race, sex, age nor BMI were associated with OS.

Survival analysis of ATAD3 mRNA levels with OS. *ATAD3A*, *ATAD3B* and *ATAD3C* mRNA expression data were available for all patients from the TCGA database. The patients were divided into two groups based on the 50% cut-off level for each mRNA. The correlations between each gene and OS were analyzed. The results indicated that the expression level of *ATAD3A* (P=0.017, HR=1.54, 95% CI=1.08-2.20; adjusted P=0.032; adjusted HR=1.52; 95% CI=1.04-2.22) and *ATAD3B* (P=0.026, HR=1.49, 95% CI=1.05-2.13; adjusted P=0.031, adjusted HR=1.52, 95% CI=1.04-2.21) were significantly correlated with OS (Table II; Fig. 2A and B). *ATAD3C* expression level was not significantly associated with OS (Table II; Fig. 2C). Furthermore, a joint-effects analysis of *ATAD3A* and *ATAD3B* with OS was performed, which demonstrated that patients with high expression levels of both *ATAD3A* and *ATAD3B* had a worse OS compared with those with low expression levels of *ATAD3A* and *ATAD3B* (P=0.007, HR=1.77,

Table I. Demography and clinical characteristics of 360 patients with hepatocellular carcinoma in The Cancer Genome Atlas database.

			Overall survival	
Variables	Patients (n=360)	MST (days)	HR (95% CI)	Log-rank P-value
Race				
Asian	155	NA	1.29 (0.89-1.87)	0.188
White+other	196	1,397		
Missing	9			
Sex				
Male	244	2,486	1.21 (0.84-1.73)	0.311
Female	116	1,560		
Age (years)				
<61	186	2,116	1.09 (0.77-1.54)	0.622
≥61	171	1,622		
Missing	3			
BMI				
≤25	193	2,456	0.87 (0.60-1.27)	0.473
>25	137	2,116		
Missing	30			
TNM stage				
I+II	252	2,532	2.50 (1.72-3.63)	<0.001
III+IV	87	770		
Missing	21			

Where survival rate was >50% in the Asian group, MST could not be calculated and is denoted as NA. MST, median survival time; HR, hazard ratio; 95% CI, 95% confidence interval; BMI, body mass index; NA, not available.

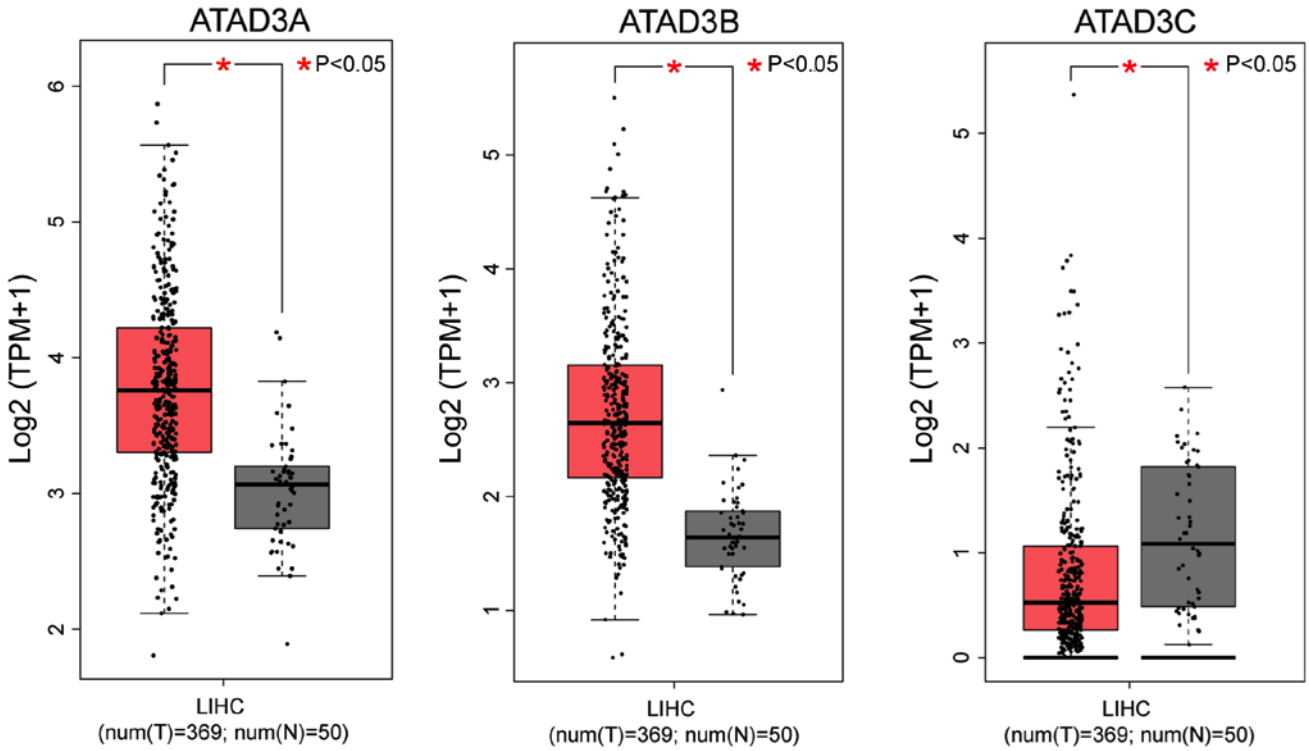

Figure 1. mRNA expression levels of *ATAD3* genes in hepatocellular carcinoma and normal liver tissues in The Cancer Genome Atlas database. Red bars denote the tumor tissue results, while grey bars denote the normal tissue results. *P<0.05 compared with normal liver tissues. *ATAD3*, ATPase family AAA domain-containing protein 3; T, tumor; N, normal; LIHC, liver hepatocellular carcinoma; TPM, Transcripts Per Million.

Table II. Prognostic survival analysis of *ATAD3* gene expression in The Cancer Genome Atlas database.

Gene	Patients (n=360)	No. of events (%)	MST (days)	HR (95% CI)	P-value	Overall survival	
						Adjusted HR (95% CI)[a]	Adjusted P-value[a]
ATAD3A							
Low	180	52 (28.9)	2,456	1.54 (1.08-2.20)	0.017	1.52 (1.04-2.22)	0.032
High	180	74 (41.1)	1,386				
ATAD3B							
Low	180	55 (30.6)	2,131	1.49 (1.05-2.13)	0.026	1.52 (1.04-2.21)	0.031
High	180	71 (39.4)	1,386				
ATAD3C							
Low	180	61 (33.9)	1,791	1.00 (0.70-1.42)	0.993	0.88 (0.61-1.27)	0.490
High	180	65 (36.1)	1,685				

[a]Adjusted for sex, age, tumor stage. MST, median survival time; *ATAD3*, ATPase family AAA domain-containing protein 3; HR, hazard ratio; 95% CI, 95% confidence interval.

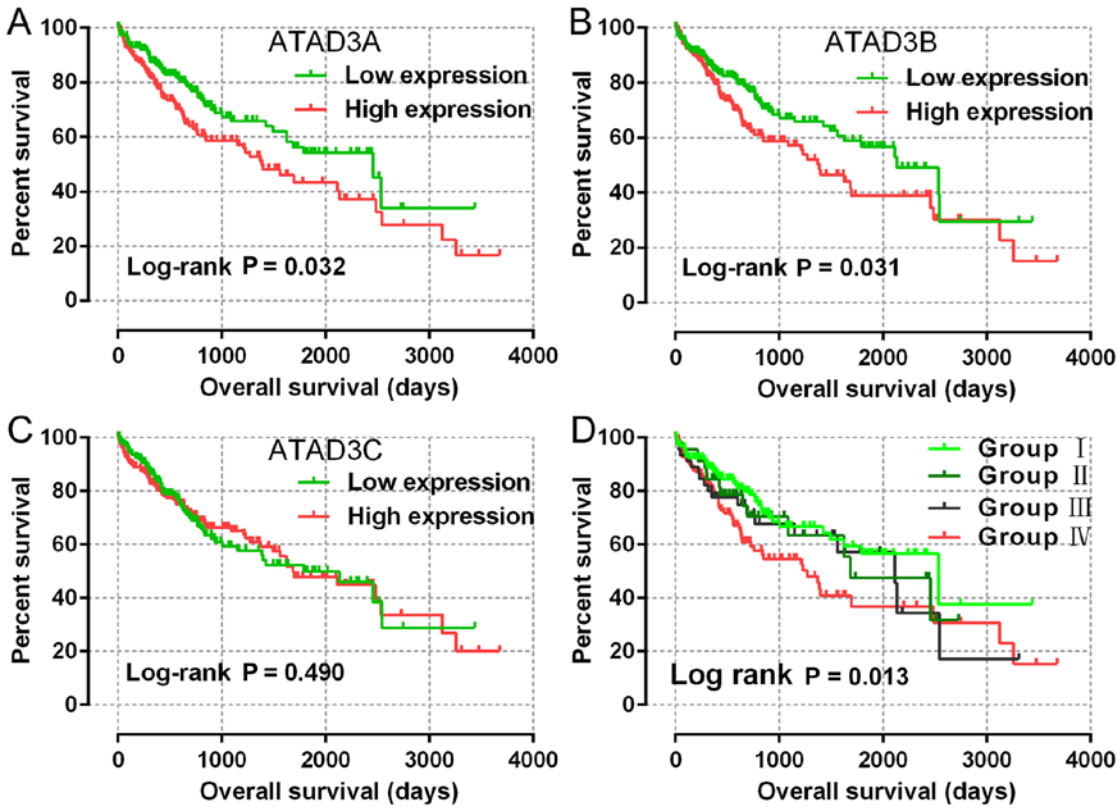

Figure 2. Survival curves for *ATAD3* gene expression in TCGA database. Survival curves of (A) *ATAD3A*, (B) *ATAD3B* and (C) *ATAD3C*. (D) Survival curves for joint-effects analysis of the combinations of ATAD3A and ATAD3B in TCGA database. TCGA, The Cancer Genome Atlas; *ATAD3*, ATPase family AAA domain-containing protein 3.

95% CI=1.16-2.69; adjusted P=0.013, adjusted HR=1.76, 95% CI=1.13-2.75) (Table III; Fig. 2D).

GO functional analysis of ATAD3 genes. KEGG pathway analysis revealed that the *ATAD3* gene cluster was associated with ATP binding, cell growth and cell division. Particularly, ATAD3A was a possible negative regulator of apoptosis (Table IV). Biological networks constructed by Cytoscape indicated that *ATAD3* genes serve important roles in ATP binding, nucleoside binding, nucleotide binding, purine nucleotide and ribonucleotide binding, adenyl nucleotide and ribonucleotide binding, catalytic activity, hydrolase activity, pyrophosphatase activity and nucleoside-triphosphatase activity (Fig. 3).

Table III. Joint-effects analysis of the combination of *ATAD3A* and *ATAD3B* expression in The Cancer Genome Atlas database.

							Overall survival	
Group	ATAD3A	ATAD3B	Patients (n=360)	MST (days)	HR (95% CI)	P-value	Adjusted HR (95% CI)[a]	Adjusted P-value[a]
I	Low	Low	133	2,532	N/A	0.060	N/A	0.102
II	Low	High	47	1,685	1.24 (0.68-2.26)	0.482	1.50 (0.80-2.84)	0.211
III	High	Low	47	2,116	1.32 (0.75-2.32)	0.333	1.49 (0.80-2.78)	0.210
IV	High	High	133	1,271	1.77 (1.16-2.69)	0.007	1.76 (1.13-2.75)	0.013

Group I, low *ATAD3A* and *ATAD3B* expression; Group II, low *ATAD3A* and high *ATAD3B* expression; Group III, high *ATAD3A* and low *ATAD3B* expression; and Group IV, high *ATAD3A* and *ATAD3B* expression. [a]Adjusted for sex, age, tumor stage. MST, median survival time; *ATAD3*, ATPase family AAA domain-containing protein 3; HR, hazard ratio; 95% CI, 95% confidence interval.

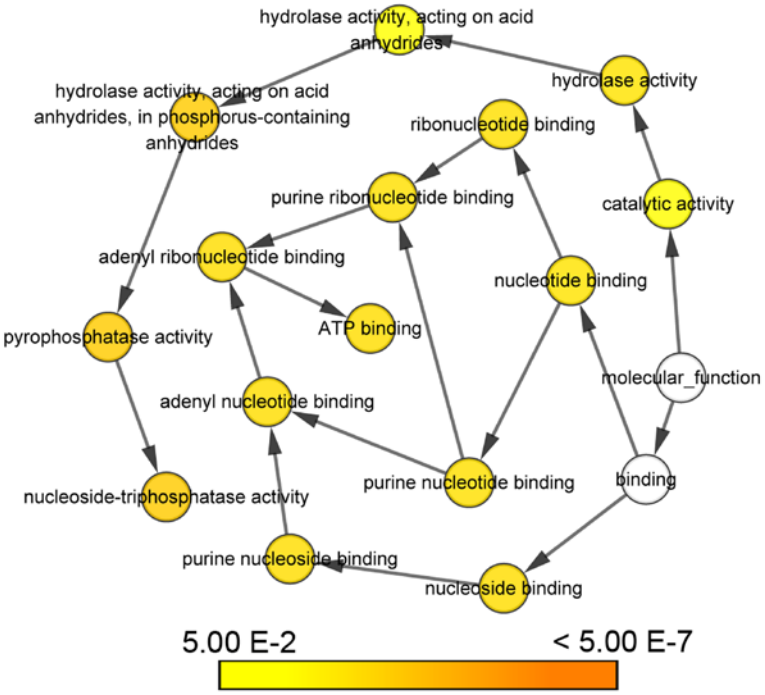

Figure 3. Functional analysis of ATPase family AAA domain-containing protein 3 genes constructed by Cytoscape.

Discussion

ATAD3, a member of the ATPase family, is exclusively present in multicellular eukaryotes at the interface between the outer and inner mitochondrial membranes, where it controls mitochondrial dynamics, mitochondrial fission, proliferation, and cholesterol transport (16,29,30). In particular, one cellular function of *ATAD3* is protecting mtDNA integrity in multicellular organisms (14,16). A number of studies have demonstrated that *ATAD3* is linked to the progression of various malignancies, including non-Hodgkin's lymphoma (21), lung adenocarcinoma (22), uterine cervical cancer (23) and prostate cancer (24). However, to the best of our knowledge, there have been no previous reports that have identified the association of *ATAD3* with HCC. Therefore, this is the first study to indicate an association between *ATAD3* expression and HCC outcomes.

In the present study, the expression of all *ATAD3* genes, including *ATAD3A*, *ATAD3B* and *ATAD3C*, was analyzed with regard to the prognosis of patients with HCC from TCGA database. The results indicated that *ATAD3A* and *ATAD3B* expression were significantly associated with OS in HCC. High *ATAD3A* expression or high *ATAD3B* expression were associated with poor MST and OS in patients with HCC. In addition, a joint-effects analysis demonstrated that patients with high *ATAD3A* and *ATAD3B* expression had reduced MST and OS rates. However, the mechanism underlying the poor survival of patients with HCC with high *ATAD3A* and *ATAD3B* expression requires further investigation.

ATAD3A is the human homologue of murine TOB3 (20), which controls mitochondrial dynamics at the interface of the inner and outer mitochondrial membranes and regulates diverse cellular responses including growth, cholesterol channeling and mitochondrial fission (16). ATAD3A has been reported

Table IV. Gene ontology analysis of *ATAD3* genes.

Gene	Category	Term	Description
ATAD3A	BP	0016049	Cell growth
	BP	0043066	Negative regulation of apoptotic process
	CC	0005739	Mitochondrion
	CC	0005743	Mitochondrial inner membrane
	CC	0016021	Integral component of membrane
	CC	0042645	Mitochondrial nucleoid
	MF	0005524	ATP binding
ATAD3B	BP	0051301	Cell division
	CC	0005743	Mitochondrial inner membrane
	MF	0005524	ATP binding
ATAD3C	MF	0005524	ATP binding

ATAD3, ATPase family AAA domain-containing protein 3; CC, cellular component; MF, molecular function; BP, biological process.

to indirectly interact with mtDNA, and silencing of *ATAD3A* increases the condensation and decreases the multimerization of mtDNA (14). A report indicated that *ATAD3A* was overexpressed in lung adenocarcinoma samples and associated with significantly higher tumor recurrence and increased drug resistance, and that silencing *ATAD3A* increased apoptosis in lung adenocarcinoma cells (22). Another study suggested that *ATAD3A* was highly expressed in prostate cancer, and that downregulating *ATAD3A* expression reduced prostate-specific antigen secretion and cisplatin resistance (24). ATAD3A is also associated with HPV infection, reduced autophagy and apoptosis, and increased drug resistance in uterine cervical cancer (23) Additionally, *ATAD3B*, which is a c-MYC and myogenin target gene, was reported to serve important roles in tumor progression (8).

Regarding *ATAD3B*, a study demonstrated that this family member was downregulated in radiation-treated Raji B cells and was associated with proliferation and apoptosis inhibition (21). Another study reported that higher *ATAD3B* expression was associated with poor survival in breast cancer and that ATAD3B was activated through estrogen receptor-α-mediated, non-genomic, MAPK-regulated transcription factors, including myogenin and c-Myc (31). Notably, one study suggested that *ATAD3B* overexpression results in loss-of-function of endogenous *ATAD3A* (32). This was corroborated by a study that indicated ATAD3B, as a human embryonic stem cell-specific mitochondrial protein, negatively regulated *ATAD3A* and acted as an adaptor of mitochondrial homeostasis and metabolism in human embryonic stem cells and lung carcinoma cells (33). In the present study, gene function network analysis also indicated that *ATAD3A* negatively regulated apoptotic processes. *ATAD3C* has been reported to have 87% homology with *ATAD3A* and is also associated with tumor progression (11). However, to the best of our knowledge, no studies have reported that *ATAD3C* expression levels are associated with the prognosis of human patients with cancer. In the current study, *ATAD3C* was not significantly associated with patient survival with HCC.

In conclusion, previous studies have reported that *ATAD3A* and *ATAD3B* are associated with tumor progression, likely due to their roles in proliferation, apoptosis, autophagy and increasing drug resistance (11,22,23). The present study's gene network analysis also revealed that the ATAD3 protein family was associated with cell growth, cell division and apoptosis. Results also demonstrated that *ATAD3A* and *ATAD3B* expression levels were significantly associated with the prognosis of patients with HCC. The present study revealed that *ATAD3A* and *ATAD3B* may serve as potential biomarkers for predicting the prognosis of patients with HCC. However, experimental and multi-center studies of *ATAD3* are required to further confirm the present study's results.

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Availability of data and materials

The datasets used during the present study are available from the corresponding author upon reasonable request.

Authors' contributions

BY, XL and GL designed the study. LA, QY and TY analyzed the data and interpreted the results. XL and GL wrote the manuscript. BY edited the manuscript. All authors discussed the results and approved the final version of the manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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