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Original Article

Serum *ARID1A* acts as a potential diagnostic biomarker for gastric cancer

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Abstract: Background: AT-rich interactive domain 1A gene (*ARID1A*) had been reported to act as a tumor suppressor in gastric cancer (GC), and reduced expression of *ARID1A* is significantly correlated with lymphatic invasion and lymph node metastasis. However, its diagnostic value in GC remains unknown. The aim of this study was to detect the expression of serum *ARID1A* and investigate its diagnostic value in GC. Methods: *ARID1A* mRNA and protein expression were assessed in 120 GC serum samples and 70 healthy control samples by quantitative real-time polymerase chain reaction (qRT-PCR) and ELISA, respectively. And the association between *ARID1A* expression and clinicopathologic parameters was evaluated by Chi-square test. To detect the diagnostic value of serum *ARID1A*, receiver operating characteristic (ROC) curve were established. Results: The expression of *ARID1A* was down-regulated in GC serum compared to that in healthy controls both at mRNA and protein level (P<0.001), and its low expression was closely related to tumor size, tumor grade, depth of invasion and lymph node metastasis. Besides, *ARID1A* expression in serum were significantly correlated with the expression of *CA19-9* (P=-0.612, P<0.001) and *CEA* (P=-0.635, P<0.001) in GC. ROC curve showed the AUC of *ARID1A* for the diagnosis of GC was 0.846 which was higher than that of *CA19-9* (0.626) and carcinoembryonic antigen (*CEA*) (0.706). Conclusions: *ARID1A* expression decreases in serum of GC patients, and it can be a useful marker for the diagnosis of GC to distinguish GC patients from noncancerous cohorts.

Keywords: *ARID1A*, gastric cancer, diagnosis, *CEA*, *CA19-9*

Introduction

Gastric cancer (GC) is the third most common type of cancers and the leading cause of cancer-associated mortality worldwide [1]. In China, there were about 300,000 deaths caused by GC each year [2]. The mechanism of GC involves a complex multi-factorial and multi-stage process that depends on interactions between gene and environment [3]. Currently, curative treatments and early diagnosis are associated with increased survival outcomes of GC patients. However, the majority of GC cases are diagnosed at later stages which lead the 5-year survival rate is only 11-40% [4]. Standard biomarkers such as carbohydrate antigen (CA) *724*, *CA19-9* and carcinoembryonic antigen (*CEA*) are useful for gastric cancer detection [5, 6], but the utility of these tumor markers are limited due to low sensitivity and specificity [7]. Therefore, new available biomarkers for the diagnosis of gastric cancer need to be detected.

AT-rich interactive domain-containing protein 1A (*ARID1A*), known as BAF250a, SMARCF1, or p270, belongs to a family of proteins containing a highly conserved about 100 amino acid DNA binding domain named *ARID* (AT-rich interacting domain) [8]. AS a member of SWI/SNF complexes, *ARID1A* is encoded by the *ARID1A* gene which is located on chromosome 1p36 [9], and contribute to specific recruitment of its chromatin remodeling activity by binding transcription factors and transcriptional coactivator/corepressor complexes [10]. The down-regulation of *ARID1A* can result in dysfunction of the SWI/SNF complex, and inhibit transcription of various genes. In addition, *ARID1A* has shown to be in involved in protein-protein interactions with sequence motif of LXXLL and cellular development, differentiation and proliferation [11, 12].

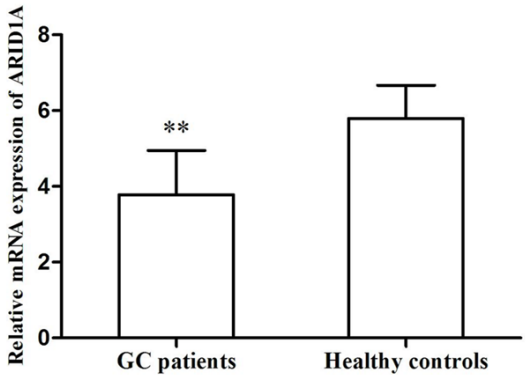

Figure 1. Relative mRNA expression of *ARID1A*. The mRNA expression of *ARID1A* in GC serum was significantly lower than that in healthy control specimens ($P<0.001$).

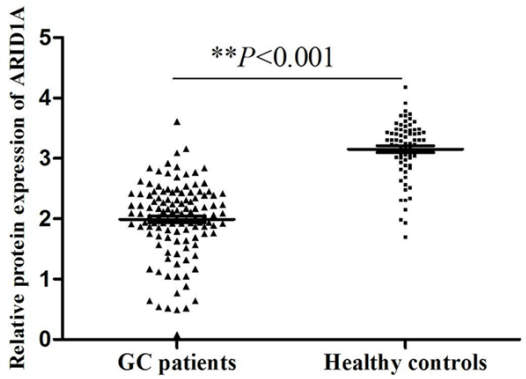

Figure 2. Relative protein expression of *ARID1A*. The protein expression of *ARID1A* in GC serum was significantly decreased compared with that in healthy control specimens ($P<0.001$).

Usually, *ARID1A* play a novel tumor suppressor role in many different cancers such as hepatocellular carcinoma and esophageal squamous cell carcinoma [13, 14]. However, its role in the diagnosis of GC remains unknown.

In this study, we detected the expression of *ARID1A* in 120 serum samples of GC and 70 healthy controls by qRT-PCR and ELISA, respectively. Moreover, its relationship with clinical factors of GC was analyzed. What's more, the diagnostic value of *ARID1A* in GC was estimated.

Materials and methods

Patients and specimens

The study was conducted at Wuhan University and approved by the Ethics Committee of the Wuhan University. 120 patients who were diagnosed with GC were collected during 2012 to 2014. None of them had received any radio- or chemo-therapy before sampling. Besides, 70 healthy people were recruited as healthy controls. All participants signed written informed consents in advance.

5 ml blood from each sample was obtained for serum isolation. All blood samples were stranded for 1 h and centrifuged for 10 min at 3000 rpm. Then they obtained serum samples were stored at -80°C till use, respectively. In addition, the clinical parameters of each patients were recorded in a database.

RNA extraction and qRT-PCR analysis

Total RNA was isolated from the serum samples with TRIzol LS reagent (Invitrogen, San Diego, CA, USA) according to the manufacturer's instructions, respectively. Only those samples of RNA with an OD A260/A280 ratio close to a value of 2.0 were available. The first chain of cDNA was synthesized using TaqMan MicroRNA Reverse Transcription Kit (Applied Biosystems, Foster City, CA, USA). RT-PCR reaction was conducted in 7300 Real-Time PCR system (Applied Biosystems) according to the manufacturer's protocol. *GAPDH* was taken as internal control. The sequences of primers for *ARID1A* and *GAPDH* were as follows: *ARID1A*: forward-5'-CTTCAACCTCAGTCAGCTCCCA-3' and reverse-5'-GGTCACCCACCTCATA-CTCCTTT-3'; *GAPDH*: forward-5'-CTCCTCCTGTTCGACAGTCAGC-3' and reverse-5'-CCCAATACGACCAAATCCGTT-3'. All reactions were performed in triplicate. Relative mRNA expression of *ARID1A* was calculated using the comparative C_T ($2^{-\Delta\Delta C_T}$) method.

ELISA analysis

Total protein was isolated from the serum of patients with GC and healthy controls. Then the serum *ARID1A*, *CEA* and *CA19-9* were measured by ELISA using ELISA kit (manufactured by Panomics Inc.) according to the manufacturer's instructions.

Statistical analysis

The statistical analyses were performed with software of SPSS version 13.0 (SPSS Inc, Chicago, IL, USA), and all data were presented as the mean ± standard deviation (SD). Stu-

Table 1. Association of *ARID1A* expression with clinicopathological parameters in GC patients

Parameters	Cases (n=120)	Serum *ARID1A* expression (Mean ± SD)	*P*
Age			0.232
≥60	65	3.68±0.54	
<60	55	3.89±0.46	
Gender			0.197
Female	52	3.80±0.37	
Male	68	3.76±0.29	
Tumor size			0.032
≥3 cm	69	3.47±0.44	
<3 cm	51	4.20±0.25	
Depth of invasion			0.009
Early	56	3.91±0.31	
Advanced	64	3.67±0.41	
Tumor grade			0.003
1, 2	60	3.84±0.36	
3	60	3.72±0.51	
Lymph node metastasis			0.008
Positive	50	3.74±0.29	
Negative	70	3.81±0.41	

dent's t-test was used to assess statistical differences of serum *ARID1A* expression between two groups. The relationship between *ARID1A* expression and clinical factors of patients with GC was analyzed by chi-square test. Spearman correlation test was used to evaluate the association between *ARID1A* expression and the expression of *CEA* or *CA19-9* in GC. The feasibility of serum *ARID1A* as a diagnostic tool for detecting GC was assessed by establishing ROC curve. $P<0.05$ was considered to be statistically significant.

Results

Down-regulation of serum ARID1A was found in GC

Normalized to GAPDH, the serum *ARID1A* mRNA expression was determined by qRT-PCR assays in 120 GC serum samples and 50 healthy controls. As results showed that, the relative mRNA expression of serum *ARID1A* in GC was significantly decreased compared to that in normal healthy specimens (3.78±1.17 vs. 5.79±0.87, $P<0.001$, **Figure 1**). Meanwhile, the protein expression of serum *ARID1A* was measured by ELISA analysis. The result demonstrated that protein expression of serum *ARID1A* was also distinctively lower in patients with GC than that in healthy controls (**Figure 2**, 1.99±0.61 vs. 3.15±0.49, $P<0.001$).

Relationship between ARID1A expression and clinicopathological features in patients with GC

To explore whether *ARID1A* was involved in the development of GC, we analyzed its relationship with clinicopathological features. As shown in **Table 1**, low *ARID1A* expression in GC was significantly associated with tumor size ($P=0.032$), tumor grade ($P=0.003$), depth of invasion ($P=0.009$) and lymph node metastasis ($P=0.008$). Concretely, lower *ARID1A* expression was more frequently detected in GC with tumor size (≥3 cm), advanced depth of tumor invasion and positive lymph node metastasis. However, there were no association of *ARID1A* expression with and age ($P=0.232$) and gender ($P=0.197$).

Diagnostic value of ARID1A in GC

ROC curve was constructed to determine the ability of serum *ARID1A* in discriminating GC patients from normal cohorts. Additionally, the diagnostic value of *CA19-9* and *CEA* were both evaluated respectively, too. As shown in **Figure 3**, the AUC of *CA19-9* and *CEA* was severally 0.626 and 0.706 while that of *ARID1A* was 0.846. This indicated that the diagnostic value of *ARID1A* was higher than that of *CA19-9* and *CEA*. Besides, *ARID1A* has a high sensitivity and specificity (80% and 77%). Furthermore, multivariable logistic regression analysis revealed that serum *ARID1A* could be a potential reliable diagnostic biomarker for patients with GC (OR=3.265, 95% CI=1.597-6.675, $P<0.001$, **Table 2**).

Correlation between serum ARID1A expression and CEA or CA19-9 expression

Next, we explored the relationship between *ARID1A* expression and the expression of *CEA* or *CA19-9* in GC samples. Spearman's correlation analysis revealed that *ARID1A* expression in serum were significantly correlated with that of *CEA* ($P=-0.635$, $P<0.001$, **Figure 4A**) and *CA19-9* ($P=-0.612$, $P<0.001$, **Figure 4B**).

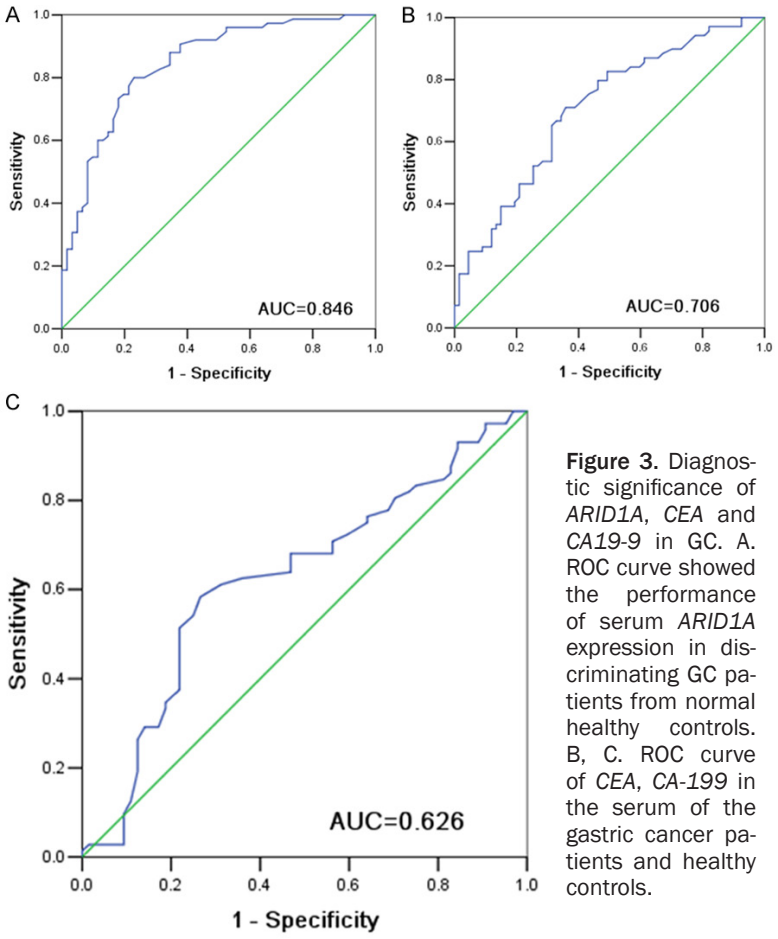

Figure 3. Diagnostic significance of *ARID1A*, *CEA* and *CA19-9* in GC. A. ROC curve showed the performance of serum *ARID1A* expression in discriminating GC patients from normal healthy controls. B, C. ROC curve of *CEA*, *CA-199* in the serum of the gastric cancer patients and healthy controls.

Table 2. Multivariable logistic regression analyses for estimating the diagnostic value of serum *ARID1A* in GC

Parameters	OR (95% CI)	*P* value
Age, ≥60 vs. <60	1.634 (0.799-3.341)	0.178
Gender, female vs. male	1.015 (0.495-3.341)	2.084
Serum *ARID1A*, ≥3.78 vs. <3.78	3.265 (1.597-6.675)	0.001

Discussion

The high incidence and mortality rates of GC were influenced by many factors such as ineffective screening, diagnosis, and treatment approaches [15, 16]. Despite molecular many markers of early diagnosis such as special genes, *lncRNAs* and *miRNAs* had been confirmed for GC detection in previous studies, the low sensitivity and specificity still made the diagnosis of GC inaccurate and not in time [17]. Thus, more effective biomarkers for GC early diagnosis are urgently needed.

ARID1A usually plays an important role in many cancers development with alterations in *ARID1A* gene or dysregulation of *ARID1A* expression. During the past researches, *ARID1A* gene has been classified as a novel tumor suppressor with loss expression in endometrial carcinomas, lung cancers and renal cancers [18-20]. Specifically, *ARID1A* could modulate cell-cycle-related genes, such as *CDKN1A* (*p21*), *SMAD3*, *C-MYC* and *E2F* to suppress tumor cellular proliferation [21-23]. Moreover, reduced *ARID1A* expression was considered to be caused by *ARID1A* frame shift and nonsense mutations. Currently, mutations of *ARID1A* were also found in various of cancers such as colon and rectal cancer, bladder cancer, pancreatic cancer, renal carcinoma, Barrett's esophagus, large B-cell lymphoma, endometrial tumors [24-30]. Concretely, these mutations could lead to mRNA decay, protein folding incorrectly or functional defects. In GC, down-regulation expression of *ARID1A* was verified to be significantly associated with lymphatic invasion and lymph node metastasis [31, 32], and this expression pattern could enhance gastric cancer cell migration and invasion via downregulation of E-cadherin transcription [33]. Functional studies revealed that the reduced expression of *ARID1A* was associated with poor prognosis in primary GC or in GC [34, 35]. However, whether *ARID1A* could be a diagnostic biomarker for GC has not been reported so far.

In the present study, our results indicated that *ARID1A* expression was significantly reduced in GC serum samples compared to that in normal healthy controls, which was consistent with previously published reports [35]. This might reveal that *ARID1A* could be a tumor suppressor in GC. And the reduced *ARID1A* expression was associated with larger tumor, advanced depth of tumor invasion and positive lymph node

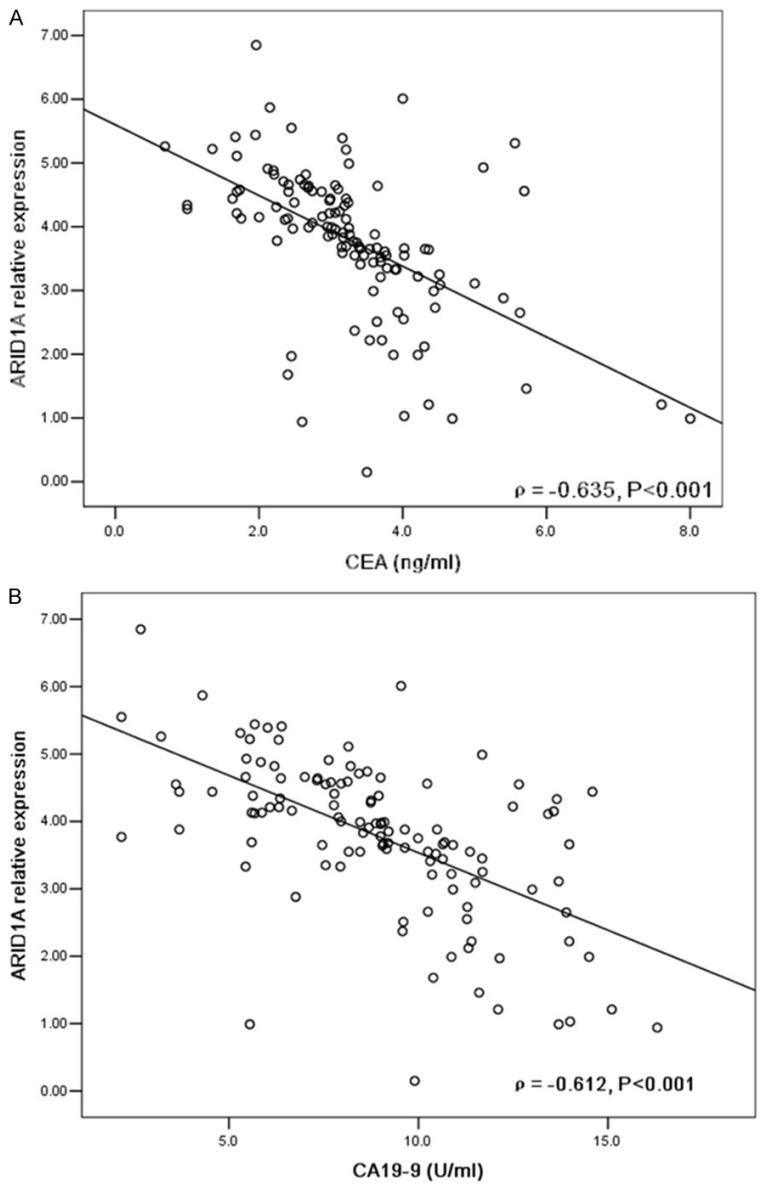

Figure 4. Correlation of the *ARID1A* with *CEA* (A) and *CA19-9* (B) in GC patients.

metastasis via chi-square test which indicated *ARID1A* was related to the development of GC.

Then we further explored the diagnostic value of *ARID1A*. ROC curves and multivariable logistic regression analyses manifested that serum *ARID1A* could distinguish GC patients from normal cohorts and could be used as a potential reliable biomarker for the clinical diagnosis of GC, which has not been reported so far. On the basis of previous studies, we further observed the predictive values of *CEA* and *CA19-9*, and found *ARID1A* had a more accurately diagnostic value. As classical biomarkers, *CEA* and *CA19-9* have previously been the commonly used markers in GC, however, they could be detected in different types of carcinoma with exhibiting low specificity and sensitivity [17]. Additionally, we determined the first study to exam the correlation of expression between *ARID1A* and *CA19-9* or *CEA*. The results showed that with upregulation of *CA19-9* or *CEA* expression, *ARID1A* expression was significantly decreased. But weather *CA-19-9* or *CEA* attenuated *ARID1A* expression in GC serum, our studies were no involved.

In summary, our findings confirm that *ARID1A* expression is decreased in GC, and it can be a potential diagnostic biomarker for GC. However, it is still necessary to detect new evidence for the diagnostic value of *ARID1A* in GC.

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Disclosure of conflict of interest

None.

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