Prognostic Significance of ACP5 in Human Gastric Cancer

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\textbf{Keywords}
ACP5 - Gastric cancer - Survival analysis - Prognostic significance

\textbf{Abstract}

\textbf{Introduction:} Tartrate-resistant acid phosphatase (ACP5) plays crucial roles in multiple pathological processes, including the genesis and progression of malignant tumors. We performed this study with the purpose of determining whether ACP5 is a crucial biomarker significantly related to prognoses of gastric cancer (GC) patients. \textbf{Methods:} The expression level of ACP5 level was assessed among 170 GC specimens using immunohistochemistry. The associations between ACP5 expression and clinicopathological variables were evaluated. Univariate and multivariate Cox regression analyses were performed to confirm independent prognostic factors for GC patients. \textbf{Results:} It was revealed that ACP5 expression level in GC tissue was significantly associated with depth of invasion ($p = 0.029$) and TNM stage ($p = 0.036$). ACP5 was demonstrated by multivariate Cox regression analysis to be an independent prognostic factor for overall survival (OS) ($p = 0.001$) and recurrence-free survival (RFS) ($p = 0.011$) of GC patients. \textbf{Conclusions:} The expression of ACP5 in GC tissue was significantly higher than that in normal tissues, and its overexpression was associated with a poorer prognosis, suggesting its potential roles in preventing and treating GC.

\textbf{Introduction}

Globally, gastric cancer (GC) is a common kind of malignant tumor with one of the highest mortality rates, especially in China since almost half of all the GC patients are diagnosed in China [1, 2]. The survival of GC patients remains not so satisfying despite the much progress made in diagnosis and treatment. Curative surgery remains the cornerstone of treating GC although other methods have been extensively investigated. However, recurrences after curative surgery still significantly limit long-term survival of GC patients. Thus, it is still an important task for us to identify novel biomarkers that are significantly related to prognoses of GC patients.
GC metastasis contributes the most to cancer-related mortality. Metastasis is a complicated, multistep process involving a series of signaling pathways. Tartrate-resistant acid phosphatase (ACP5) has been extensively investigated in malignant tumors [3–5]. It has been proven by these studies that ACP5 is one of the most frequently overexpressed oncogenes in multiple solid tumors. It has been reported that ACP5 is associated with progression and metastasis of malignant tumors [5]. Interestingly, Kawamura et al. [5] reported that ACP5 was predictive of peritoneal dissemination for patients with GC and might play key roles in the pathogenesis of peritoneal metastasis. However, the role of ACP5 in patients without peritoneal metastasis has not been fully uncovered. In the current study, we performed immunohistochemistry (IHC) to investigate the potential roles of ACP5 in occurrence and progression of GC.

Materials and Methods

Study Design and Ethical Approval
This single-institution retrospective study evaluated the data of patients with GC who received curative gastrectomy at The First Affiliated Hospital, Sun Yat-sen University. Declaration of Helsinki was adhered to during the whole process of this study. The present study was approved by the Ethical Committee of The Seventh Affiliated Hospital, Sun Yat-sen University and The First Affiliated Hospital, Sun Yat-sen University. All the patients gave their written informed consents before surgery.

Study Population
Data of patients receiving surgery between January 2009 and December 2013 were retrospectively collected. Patients meeting one of the following criteria were excluded from this study: receiving palliative surgery; receiving neoadjuvant therapy (radiotherapy, chemotherapy, or both); lost during the early phase of follow-up; with incomplete clinicopathological data; diagnosed with other type of GC such as squamous cell carcinoma and adenosquamous carcinoma. The follow-ups were terminated on December 2019. A total of 170 patients with complete clinicopathological data were included in our study. Clinical information of each patient such as age, gender, operation type, tumor size, Borrmann classification, differentiation, depth of invasion, lymph node metastasis, TNM stage, CEA level, and vessel or nerve invasion was obtained from his or her medical record. The eighth edition of the American Joint Committee on Cancer (AJCC)/International Union Against Cancer TNM classification system was adopted to determine tumor stages.

Bioinformatics Analysis
In order to investigate the expression of ACP5 in GC, we downloaded data from The Cancer Genome Atlas (TCGA) database (https://cancergenome.nih.gov) and performed statistical analyses. The expression levels of ACP5 in GC tissues were compared with those in normal tissues. The associations between ACP5 expression and clinical variables were also analyzed. The expression levels of ACP5 in different GC cell lines were also investigated by bioinformatics methods.

IHC and Scoring
IHC was performed to assess the expression levels of ACP5 in GC tissues. According to the manufacturer’s instructions, a ACP5-specific antibody purchased from Proteintech group (11594-1-AP; Wuhan, Hubei, China) was used in IHC staining. GC tissue slides were initially embedded by paraffin. These slides were first deparaffinized with xylene and rehydrated with alcohol of different concentrations (100, 95, 85, and 75%). Endogenous peroxidase activity of the GC tissue was blocked with 0.3% hydrogen peroxide for 20 min. Then the slides were blocked by 10% BSA for 30 min and subsequently incubated with ACP5-specific antibodies (1:1,000) at 4°C overnight. Then on the second day, the sections were incubated with secondary antibodies that were biotinylated for half an hour at room temperature. Then 3,3-diaminobenzidine (DAB) (GK600510, Gene Tech, Shanghai, China) was used as the chromogen substrate. An inverted microscope system (Olympus, BX53, Tokyo, Japan) was used to capture the images. Ultimately, the stained slides by DAB were counterstained with hematoxylin. Two experienced pathologists without prior knowledge of patients’ clinical information independently scored the stained slides. Brown-yellow staining was indicative of ACP5-positivity. The total scores of GC slides were determined through multiplying staining intensity and percentage of positive cells. Staining intensity was classified into 0 (no staining) (shown in Fig. 1a, e), 1 (weak) (shown in Fig. 1b, f), 2 (moderate) (shown in Fig. 1c, g), and 3 (strong) (shown in Fig. 1d, h). Percentage of cells was defined according to the following criteria: 1 (1–25%), 2 (26–50%), 3 (51–75%), and 4 (76–100%). It was defined as high expression when the total score was ≥6 and low expression was defined when the total score was <6.

Statistical Analysis
The expression levels and clinicopathological variables of the 170 GC patients were compared using χ2 test and Fisher’s exact test. Survival of patients of the 2 groups was calculated by the Kaplan-Meier method and tested by the log-rank method. Overall survival (OS) was defined as the duration from curative surgery to death no matter what cause of mortality is. Recurrence-free survival (RFS) was defined as the duration from curative surgery to GC recurrence. Univariate Cox regression model analyses were performed to identify variables that were significantly associated with OS or RFS. Then variables meeting one of the following criteria were included in multivariate Cox regression model analysis to identify independent prognostic factors for GC patients: a variable with its p value <0.05 in univariate Cox regression model analysis; a variable that had been repeatedly proven by other studies to be an independent prognostic factor for GC patients despite the fact that its p value was ≥0.05 in univariate Cox regression model analysis; a variable that had been listed as an independent prognostic factor for GC patients by current guidelines despite the fact that its p value was ≥0.05 in univariate Cox regression analysis. SPSS 22 (Chicago, IL, USA) was adopted to perform all the statistical analyses. All tests of our study were two-sided in nature, and a p value <0.05 was considered statistically significant.
Results

Patients’ baseline characteristics and the associations between ACP5 expressions and these clinicopathological variables were shown in Table 1. A total of 83 (48.8%) patients received adjuvant chemotherapy. The median follow-up of the included patients in this study was 53 months (1–99 months). The expression level was significantly associated with depth of invasion ($p = 0.029$) and TNM stage ($p = 0.036$). Other variables such as age, gender, operation type, tumor size, Bormann classification, differentiation, lymph node metastasis, CEA level, and vessel or nerve invasion were, however, not found to be significantly associated with ACP5 expression.

Bioinformatics Analysis

With the purpose of investigating the expression of ACP5 in GC, we analyzed data downloaded from the TCGA database, the results of which demonstrated that compared with that in normal tissues, the expression level of ACP5 in GC was significantly higher ($p < 0.001$) (shown in Fig. 2a), which was consistent with our results. The relative expression levels of ACP5 in different GC cell lines were shown in Figure 2c.

Survival Analysis

The survival analyses revealed that the median survival time of the 170 GC patients was 39 months. Kaplan-Meier method demonstrated that the expression level of ACP5 was significantly associated with OS ($p = 0.001$) (shown in Fig. 3a) and RFS ($p = 0.011$) (shown in Fig. 3b). The univariate Cox regression analysis revealed that tumor size ($p < 0.001$, HR = 2.464, 95% CI: 1.543–3.935), depth of invasion ($p < 0.001$, HR = 7.854, 95% CI: 3.164–19.501), lymph node metastasis ($p < 0.001$, HR = 4.241, 95% CI: 2.318–7.761), TNM stage ($p < 0.001$, HR = 5.444, 95% CI: 3.144–9.427), CEA level ($p = 0.007$, HR = 2.228, 95% CI: 1.240–4.004), vessel or nerve invasion ($p < 0.001$, HR = 2.873, 95% CI: 1.740–4.745), and ACP5 expression ($p = 0.001$, HR = 2.261, 95% CI: 1.377–3.714) were significantly associated with OS (shown in Table 2). Then these aforementioned variables and gender were included in multivariate Cox regression analysis, the results of which demonstrated that depth of invasion ($p = 0.006$, HR = 3.967, 95% CI: 1.473–10.679), lymph node metastasis ($p = 0.043$, HR = 2.047, 95% CI: 1.023–4.098), and

![Fig. 1. Different expression intensities of ACP5 in GC tissues assessed by IHC staining. (×20) (a) and (×40) (e) stands for no staining, (×20) (b) and (×40) (f) stands for weak staining, (×20) (c) and (×40) (g) stands for moderate staining, and (×20) (d) and (×40) (h) stands for strong staining. ACP5, tartrate-resistant acid phosphatase; GC, gastric cancer; IHC, immunohistochemistry.](image-url)
ACP5 expression ($p = 0.008$, HR = 2.033, 95% CI: 1.204–3.433) were independent predictive factors for OS of GC patients (shown in Table 2).

Similarly, it was revealed through univariate Cox regression analysis that tumor size ($p = 0.001$, HR = 2.563, 95% CI: 1.435–4.578), differentiation ($p = 0.014$, HR = 2.590, 95% CI: 1.209–5.550), depth of invasion ($p < 0.001$, HR = 7.077, 95% CI: 2.537–19.742), lymph node metastasis ($p < 0.001$, HR = 4.699, 95% CI: 2.191–10.079), TNM stage ($p < 0.001$, HR = 5.822, 95% CI: 2.947–11.501), CEA level ($p = 0.044$, HR = 2.115, 95% CI: 1.021–4.380), vessel or nerve invasion ($p < 0.001$, HR = 4.104, 95% CI: 2.268–7.425), and ACP5 expression ($p = 0.013$, HR = 2.149, 95% CI: 1.175–3.930) were significantly associated with RFS (shown in Table 3). Then, these variables significantly associated with RFS and gender were included in multivariate Cox regres-

### Table 1. Associations of ACP5 expression with clinical parameters in GC

| Characteristic               | N   | ACP5 expression | p value |
|-----------------------------|-----|-----------------|---------|
|                            |     | low (N = 85)    | high (N = 85) |
| Age, years                  |     |                 |         |
| ≤60                         | 99  | 57.8±11.3       | 57.2±12.7 | 0.756 |
| >60                         | 71  | 51              | 48      |
| Gender                      |     |                 |         |
| Male                        | 124 | 65              | 59      | 0.388 |
| Female                      | 46  | 20              | 26      |
| Operation type              |     |                 |         |
| Distal gastrectomy          | 89  | 45              | 44      | 1.000 |
| Total gastrectomy           | 81  | 40              | 41      |
| Tumor size                  |     |                 |         |
| ≤5 cm                       | 121 | 64              | 57      | 0.310 |
| >5 cm                       | 49  | 21              | 28      |
| Bormann classification      |     |                 |         |
| I + II                      | 66  | 37              | 29      | 0.271 |
| III + IV                    | 104 | 48              | 56      |
| Differentiation             |     |                 |         |
| Well + moderate             | 51  | 22              | 29      | 0.315 |
| Poor                        | 119 | 63              | 56      |
| Depth of invasion           |     |                 |         |
| T1                          | 29  | 18              | 11      |
| T2                          | 24  | 16              | 8       |
| T3                          | 58  | 27              | 31      | 0.029 |
| T4a                         | 38  | 14              | 24      |
| T4b                         | 21  | 10              | 11      |
| Lymph node metastasis       |     |                 |         |
| N0                          | 66  | 32              | 34      |
| N1                          | 29  | 20              | 9       |
| N2a                         | 33  | 18              | 15      | 0.208 |
| N2b                         | 24  | 12              | 12      |
| N3                          | 18  | 3               | 15      |
| TNM stage                   |     |                 |         |
| I                           | 43  | 27              | 16      | 0.036 |
| II                          | 45  | 23              | 22      |
| III                         | 82  | 35              | 47      |
| CEA level, μg/L             |     |                 |         |
| ≤5                          | 148 | 76              | 72      | 0.494 |
| >5                          | 22  | 9               | 13      |
| Vessel or nerve invasion    |     |                 |         |
| Yes                         | 36  | 15              | 21      | 0.348 |
| No                          | 134 | 70              | 64      |

ACP5, tartrate-resistant acid phosphatase; GC, gastric cancer.
sion analysis, the results of which demonstrated that depth of invasion ($p = 0.039$, HR = 3.320, 95% CI: 1.065–10.345), vessel or nerve invasion ($p = 0.004$, HR = 2.582, 95% CI: 1.365–4.883), and ACP5 expression ($p = 0.028$, HR = 2.409, 95% CI: 1.079–3.889) were independent predictive factors for RFS of GC patients (shown in Table 3).

**Discussion/Conclusion**

As an enzyme secreted by mature osteoclasts, ACP5 is considered as a biomarker for bone resorption and osteoclast maturation. Thus, ACP5 activity in serum could be utilized to evaluate osteolysis caused by bone metastasis.
High Expression of ACP5 Predicts Poor Prognosis

in a few kinds of human malignancies [6–9]. A few previously published studies had reported that ACP5 was able to promote metastasis and invasion of liver cancer and GC cells [5, 8]. Overexpression of ACP5 in melanoma was related to decreased focal adhesion kinase autophosphorylation at Tyr, which was believed to promote cancer cell invasion. Besides its relation with increased invasive ability of melanoma cells, overexpression of ACP5 was also reported to cause morphological changes and increase movement ability of cancer cells [10]. It was re-

Table 2. Cox proportional-hazard regression analysis for overall survival

| Characteristic                  | Univariate analysis | Multivariate analysis |
|--------------------------------|---------------------|-----------------------|
|                                | $p$ value | HR | 95% CI for exp (b) | $p$ value | HR | 95% CI for exp (b) |
|--------------------------------|-----------|----|-------------------|-----------|----|-------------------|
| Gender                         | 0.058     | 1.623 | 0.983 | 2.680 | 0.114 | 1.519 | 0.905 | 2.551 |
| Age                            | 0.603     | 1.131 | 0.710 | 1.802 |        |       |       |       |
| Operation type                 | 0.063     | 1.559 | 0.977 | 2.489 |        |       |       |       |
| Tumor size                     | <0.001    | 2.464 | 1.543 | 3.935 | 0.266 | 1.322 | 0.809 | 2.161 |
| Differentiation                | 0.030     | 1.859 | 1.062 | 3.254 | 0.232 | 1.435 | 0.794 | 2.594 |
| Depth of invasion              | <0.001    | 7.854 | 3.164 | 19.501 | 0.006 | 3.967 | 1.473 | 10.679 |
| Lymph node metastasis          | <0.001    | 4.241 | 2.318 | 7.761 | 0.043 | 2.047 | 1.023 | 4.098 |
| N0                             |           |       |       |       |       |       |       |       |
| N+                             |           |       |       |       |       |       |       |       |
| TNM stage                      | <0.001    | 5.444 | 3.144 | 9.427 |        |       |       |       |
| I + II                         |           |       |       |       |       |       |       |       |
| III                            |           |       |       |       |       |       |       |       |
| CEA level                      | 0.007     | 2.228 | 1.240 | 4.004 | 0.218 | 1.482 | 0.793 | 2.771 |
| Vessel or nerve invasion       | <0.001    | 2.873 | 1.740 | 4.745 | 0.058 | 1.703 | 0.983 | 2.950 |
| ACP5 expression                | 0.001     | 2.261 | 1.377 | 3.714 | 0.008 | 2.033 | 1.204 | 3.433 |
| Low                            |           |       |       |       |       |       |       |       |
| High                           |           |       |       |       |       |       |       |       |

ACP5, tartrate-resistant acid phosphatase.
ported by Xia et al. [8] that ACP5 was more highly expressed in HCC tissues than that in normal liver tissues and its overexpression was significantly associated with poorer prognoses of patients with HCC after curative hepatectomy. It was further revealed by them that ACP5 was closely related to a crucial modulator of epithelial-mesenchymal transition (EMT), forkhead box M1 (FOXM1) [8, 11, 12]. In this study by them, it was demonstrated that suppression of ACP5 expression significantly inhibited the FOXM1-mediated in vitro and in vivo metastasis of liver cancer cells, suggesting that ACP5 was an indispensable downstream target in FOXM1-mediated promoting invasiveness and metastasis of cancer cell [8]. FOXM1 had been reported to promote angiogenesis, proliferation, invasion, and metastasis of cancer cells through increasing the expression of VEGF [13, 14]. Kawamura et al. [8] reported that for GC patients, ACP5 might play a role in peritoneal dissemination and could predict peritoneal metastasis. All these aforementioned studies suggest that ACP5 is closely associated with several metastasis-related genes, and overexpression of ACP5 may lead to the formation of microenvironments promoting invasiveness and metastasis of cancer cells. As for its roles in formation of bone metastasis, ACP5 had been extensively investigated in various malignant tumors. Yao et al. [6] reported that ACP5 could be utilized as a biomarker for bone metastasis of non–small-cell lung cancer. Wu et al. [9] concluded that ACP5 was a prognostic biomarker for breast cancer patients with bone metastasis. In 2017, Wang et al. [7] reported that along with other bone metabolism markers, ACP5 could be utilized to effectively predict the efficacy of biphosphonate treatment for bone metastasis of patients with breast cancer. Thus, the expression level of ACP5 could be potentially used to predict the occurrence of bone metastasis of malignant tumors and response to biophosphonate treatment. In this study, of the 170 included GC patients, only 4 were diagnosed with bone metastasis after curative gastrectomy, limiting our evaluating the roles of ACP5 in formation of bone metastasis of GC. Additionally, as far as we are known, no studies on bone metastasis of GC have been published. Thus, it is necessary for us to perform more studies to illuminate the roles of ACP5 in bone metastasis of GC.

In this present study, it was proven that the expression of ACP5 in GC tissue was significantly higher than that in normal tissue and its expression was significantly associated with depth of invasion, TNM stage. As for its prog-

### Table 3. Cox proportional-hazard regression analysis for recurrence-free survival

| Characteristic                        | Univariate analysis | Multivariate analysis |
|--------------------------------------|---------------------|-----------------------|
|                                      | p value  | HR   | 95% CI for exp (b) | p value  | HR   | 95% CI for exp (b) |
|                                      |          | lower | upper             |          | lower | upper             |
| Gender                               | 0.193    | 1.505 | 0.813             | 2.784 | 0.488 | 1.255 | 0.660 | 2.386 |
| Age                                  | 0.616    | 0.860 | 0.477             | 1.549 | 0.240 | 1.443 | 0.783 | 2.660 |
| Operation type                       | 0.323    | 1.335 | 0.753             | 2.367 | 0.063 | 2.143 | 0.959 | 4.791 |
| Tumor size                           | 0.001    | 2.563 | 1.435             | 4.578 | 0.039 | 3.320 | 1.065 | 10.345 |
| Differentiation                      | 0.014    | 2.590 | 1.209             | 5.550 | 0.110 | 2.043 | 0.850 | 4.909 |
| Depth of invasion                    | <0.001   | 7.077 | 2.537             | 19.742 | 0.011 | 3.240 | 0.842 | 12.604 |
| T1 + T2                              |          |       |                   |       |       |       |       |       |
| T3 + T4                              |          |       |                   |       |       |       |       |       |
| Lymph node metastasis                | <0.001   | 4.699 | 2.191             | 10.079 | 0.011 | 2.043 | 0.850 | 4.909 |
| N0                                   |          |       |                   |       |       |       |       |       |
| N+                                   |          |       |                   |       |       |       |       |       |
| TNM stage                            | <0.001   | 5.822 | 2.947             | 11.501 | 0.011 | 3.240 | 0.842 | 12.604 |
| I + II                               |          |       |                   |       |       |       |       |       |
| III                                  |          |       |                   |       |       |       |       |       |
| CEA level                            | 0.044    | 2.115 | 1.021             | 4.380 | 0.218 | 1.482 | 0.793 | 2.771 |
| Vessel or nerve invasion             | <0.001   | 4.104 | 2.268             | 7.425 | 0.449 | 1.350 | 0.621 | 2.933 |
| ACP5 expression                      | 0.013    | 2.149 | 1.175             | 3.930 | 0.004 | 2.582 | 1.365 | 4.883 |
| Low                                  |          |       |                   |       |       |       |       |       |
| High                                 |          |       |                   |       |       |       |       |       |

ACP5, tartrate-resistant acid phosphatase.
High Expression of ACP5 Predicts Poor Prognosis

The expression of ACP5 in GC tissue was significantly higher than that in normal tissues, and its overexpression was associated with a poorer prognosis, suggesting its potential roles in preventing and treating GC.

Conclusions

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Statement of Ethics

Declaration of Helsinki was adhered to during the whole process of this study. The present study was approved by the Ethical Committee of The Seventh Affiliated Hospital, Sun Yat-sen University and The First Affiliated Hospital, Sun Yat-sen University. Approval Letter for Research Protocol: No. 381 [2020]. All the patients participating in this study had given informed consents in written form.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Changhua Zhang and Tailai An designed the study. Lyujia Cheng, Yan Wang, and Wang Wu collected the data. Tailai An, Qian Liang, Lingna Deng, and Xiaofang Lu performed the IHC staining. Tengfei Hao, Qian Liang, Lingna Deng, and Xiaofang Lu scored the stained slides. Tengfei Hao, Lingna Deng, Qian Liang, and Tailai An accomplished the statistical analyses. Tailai An, Lyujia Cheng, Lingna Deng, and Yan Wang drafted and revised the manuscript. All authors read and approved of the final manuscript.

References

1 Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. CA Cancer J Clin. 2020;70(1):7–30.
2 Chen W, Zheng R, Baade PD, Zhang S, Zeng H, Bray F, et al. Cancer statistics in China, 2015. CA Cancer J Clin. 2016;66(2):115–32.
3 Shi R, Liu T, Liu Z, Yang L, Shi Y, Zhang Y. Knockdown of ACP5 inhibits hepatocellular carcinoma progression. Am J Transl Res. 2020;12(5):1904–12.
4 Hu Y, Yu J, Wang Q, Zhang L, Chen X, Cao Y, et al. Tartrate-resistant acid phosphatase 5/ACP5 interacts with p53 to control the expression of SMAD3 in lung adenocarcinoma. Mol Ther Oncolytics. 2020;16:272–88.
5 Kawamura M, Tanaka K, Toiyama Y, Okugawa Y, Okigami M, Yasuda H, et al. Clinical significance of tartrate-resistant acid phosphatase type-5 expression in human gastric cancer. Anticancer Res. 2014;34(7):4255–9.
6 Yao NS, Wu YY, Jancikla AJ, Ku CH, Hsieh AT, Ho CL, et al. Serum tartrate-resistant acid phosphatase 5b (TRACP5b) activity as a biomarker for bone metastasis in non-small cell lung cancer patients. Clin Chim Acta. 2011;412(1–2):181–5.
7 Wang R, Zhang S, Jiang Z, Tian J, Wang T, Song S. Bone metabolism markers: indicators of loading dose intravenous ibandronate treatment for bone metastases from breast cancer. Clin Exp Pharmacol Physiol. 2017;44(1):88–93.
8 Xia L, Huang W, Tian D, Chen Z, Zhang L, Li Y, et al. ACP5, a direct transcriptional target of FOXM1, promotes tumor metastasis and indicates poor prognosis in hepatocellular carcinoma. Oncogene. 2014;33(11):1395–406.
9 Wu YY, Jancikla AJ, Ku CH, Yu CP, Yu JC, Lee SH, et al. Serum tartrate-resistant acid phosphatase 5b activity as a prognostic marker of survival in breast cancer with bone metastasis. BMC Cancer. 2010;10:158.
10 Scott KL, Nogueira C, Heffernan TP, van Doorn R, Dhakal S, Hanna JA, et al. Proinvasion metastasis drivers in early-stage melanoma are oncogenes. Cancer Cell. 2011;20(1):92–103.
11 Bella L, Zona S, Nestal de Moraes G, Lam EW. FOXM1: a key oncofoetal transcription factor in health and disease. Semin Cancer Biol. 2014;29:32–9.
12 Katoh M, Igarashi M, Fukuda H, Nakagama H, Katoh M. Cancer genetics and genomics of human FOX family genes. Cancer Lett. 2013;328(2):198–206.
13 Karadedou CT, Gomes AR, Chen J, Petkovic M, Ho KK, Zwolinska AK, et al. FOXO3a represses VEGF expression through FOXM1-dependent and -independent mechanisms in breast cancer. Oncogene. 2012;31(14):1845–58.
14 Li Q, Zhang N, Jia Z, Le X, Dai B, Wei D, et al. Critical role and regulation of transcription factor FoxM1 in human gastric cancer angio genesis and progression. Cancer Res. 2009;69(8):3501–9.