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Original Article

High Rab25 expression associates with Ki67/TP53/CD133/VEGFR expression predicts poor prognosis in gastric cancer

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Abstract: Rab25 belongs to Rab GTPases which regulating vesicle trafficking of various extracellular and intracellular resources. Aberrant high Rab25 expression is closely linked to cancer development including gastric cancer. However, the underlying mechanism of Ras25 in gastric cancer is still unclear. In this study, we determined to investigate the potential association between Rab25 and four tumor markers, including Ki67 (a well-known hallmarker of tumor proliferation), TP53 (tumor p53, a master tumor regulator associated with cell apoptosis), CD133 (a common cancer stem cell marker) and VEGFR (Vascular endothelial growth factor receptor, an efficient therapy target for gastric cancer). The results indicated that Rab25 expression in both cytoplasm and nucleus was significantly higher in gastric cancer tissues than para-carcinoma tissues. High Rab25 nucleus expression was positively associated with distant metastasis (M stage) and clinical (cTNM) stage, while Rab25 nucleus expression correlated with M stage, cTNM stage and regional lymph metastasis stage (N stage). Survival analysis revealed that high Rab25 cytoplasm/nucleus expression predicted shorter overall survival time of patients with gastric cancer. Rab25 expression was significantly associated with Ki67 expression, TP53 expression, CD133 expressionand VEGFR expression in gastric cancer. In conclusion, our results indicated that Rab25 behaved as an oncogene in gastric cancer related to Ki67/TP53/CD133/VEGFR expression and suggested Rab25 to be a prognostic marker.

Keywords: Gastric cancer, Rab25, prognosis, immunohistochemistry

Introduction

Gastric cancer was one of the most common cancers all over the world. Despite the rapid evolution of treatment approaches for gastric cancer, the mortality of patients with gastric cancer in China was still high [1]. Most of the cases was diagnosed at the advantage stage while it was too late to be regional resected by surgery, which might confer high mortality of gastric cancer. Therefore, discovering new and more sensitive diagnostic and prognostic biomarkers for gastric cancer was emerging.

Rab25 belongs to Rab GTPases which regulating vesicle trafficking of various extracellular and intracellular resources [2]. Aberrant Rab25 expression might result in the perturbations of vesicle trafficking mechanism which finally contributing to some diseases including cancer. Mounting evidence showed the Rab25 involvement in cancer progression, including esophageal carcinoma, colon cancer, head and neck squamous cell carcinoma, ovarian cancer, renal carcinoma and breast cancer [3-8]. However, the biological function of Rab25 in cancer was still contradictory, acting as an oncogene and tumor suppressor, depending on context. The oncogenic function of Rab25 in gastric cancer has been proved previously [9]. However, the regulatory mechanism of Ras25 in gastric cancer is still unclear. The aim of this study was to investigate the potential regulatory mechanism according to analysis the potential association between Rab25 and four tumor markers, including Ki67 (awell-known hallmarker of tumor proliferation), TP53 (tumor p53, a master tumor

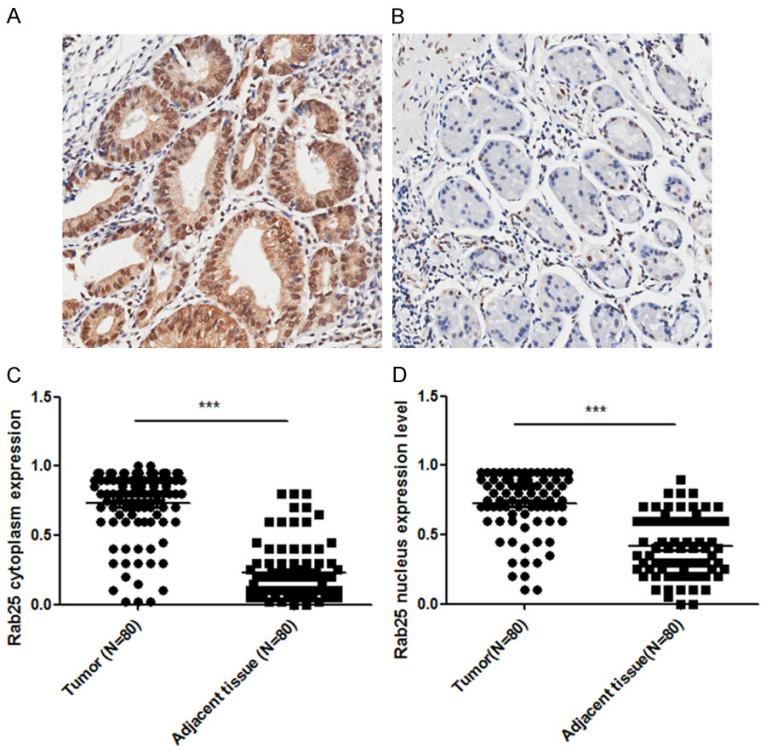

Figure 1. Rab25 expression in gastric cancer tissues and para-carcinoma tissues. Rab25 localized in both cytoplasmand nucleus in all specimens, including gastric cancer tissues (A) and para-carcinoma tissues (B) (Magnification times: ×200). Rab25 cytoplasm expression in gastric cancer tissues was significantly higher than that in para-carcinoma tissues (C), as well as Rab25 nucleus expression (D). ***P<0.001.

regulator associated with cell apoptosis), CD-133 (a common cancer stem cell marker) and VEGFR (Vascular endothelial growth factor receptor, an efficient therapy target for gastric cancer) by immunohistochemistry.

Here, we planned to study on the Rab25 expression in a cohort of gastric cancer paraffin-embedded specimensby immunohistochemistry. According to statistically analysis, the abnormal of Rab25 expression in gastric cancer as well as the correlation between Rab25 expression and clinical outcome were evaluated by systematically analysis, in order to reveal the clinical significance of Rab25 expression in gastric cancer.

Materials and methods

Clinical materials

Gastric cancer tissue microarray (HStmA180-Su08) was obtained from Shanghai Outdo Biotech Co., Ltd. (SOBC). 100 patients with gastric cancer were recruited in this study, 80 of whose corresponding para-carcinoma tissues were involved in the same TMA. The clinical information of the 100 patients with gastric cancer in this study was shown as below: 64 males and 36 females ranged the age from 32 to 81, with two missing the age information; the tumor size of these patients distributed from 1.2 cm to 20 cm; according to 7rd UICC, these patients were classified into four clinical stage, including 10 stage I, 32 stage II, 48 stage III, 8 stage IV and 2 missing clinical stage information. All these patients were diagnosed with primary gastric cancer and received no therapy before resection. After surgery dating from July 2006 to April 2007, these patients' survival situation was followed up over 8 years. Till July 2015, 71 patients were died of gastric cancer (median survival time 20 months) while 29 patients were still alive.

Immunohistochemistry

Two step immunohistochemistry was used to detect the Rab25 expression in gastric cancer tissues and para-carcinoma tissues. First, the antigen retrieval was performed by treating with citrate buffer, endogenous peroxidase activity were removed by 3% hydrogen peroxide. TMAs were incubated with goat serum and subsequently incubated with anti-Rab25 antibody (promab, 20430) at a dilution of 1:2000 at 4°C overnight, subsequently incubated with the secondary antibody (DAKO, K8000). Similarly, the expression of Ki67 (antibody, Dako, IR616), TP53 (antibody, Dako, IR626), CD133 (antibody, Promab30240) and VEGFR (antibody, MAB-0243) were investigated by the similar protocol. At least three visual fields from different areas of each specimen were chosen randomly and more than 100 cells were calculated for immunohistochemistry evaluation by pathologists. Rab25 expression was scored according to the positive rate. The cut-off point was determined by ROS curve, and the tissues

Table 1. Correlation between Rab25 cytoplasm/nucleus expression and clinical index of the patients with gastric cancer

Clinical factors	Rab25 cytoplasm expression		Coefficient	*P* value	Rab25 nucleus expression		Coefficient	*P* value
	Low	High			Low	High		
Gender			0.004	0.968			0.062	0.543
Male	50	14			53	11		
Female	28	8			28	8		
Age			0.280**	0.005			0.186	0.067
≤ 60	31	2			30	3		
> 60	45	20			49	16		
Tumor size			0.109	0.286			0.087	0.392
≤ 5 cm	41	9			42	8		
> 5 cm	35	13			37	11		
Grade			0.044	0.667			0.041	0.683
II	13	2			14	1		
III	56	18			57	17		
IV	9	2			10	1		
T stage			0.073	0.495			0.167	0.119
T1	8	0			8	0		
T2	4	3			5	2		
T3	48	12			49	11		
T4	10	4			9	5		
N stage			0.190	0.061			0.302**	0.003
N0	22	5			25	2		
N1	14	1			14	1		
N2	21	5			21	5		
N3	19	11			19	11		
M stage			0.287**	0.004			0.326**	0.001
M0	74	17			77	14		
M1	3	5			3	5		
cTNM stage			0.256*	0.011			0.359**	<0.001
1	8	2			9	1		
2	29	3			31	1		
3	36	12			36	12		
4	3	5			3	5		

*Correlation is significant at the 0.05 level (2-tailed). **Correlation is significant at the 0.01 level (2-tailed).

were divided into two subgroups according to different positive rate: positive rate ≤ 90%: low expression; positive rate > 90%: high expression.

Statistical analysis

The difference between Rab25 expression in gastric cancer and in para-carcinoma was calculated by Pared T-Test. The association between Rab25 cytoplasm expression and Rab25 nucleus expression evaluated by Pearson correlation coefficients, and so does the correlation between Rab25 cytoplasm/nucleus and TP53 expression, Ki67 expression, CD133 expression as well as VEGFR expression. The correlation between Rab25 expression and the clinical factors was calculated by Spearman rank correlation coefficients. Survival curve was evaluated by Kaplan-Meier method and log-rank test. COX multivariate regression survival analysis was done involved all the potential predict factors. SPSS 17.0 software was used for all statistically analyzed, and $P<0.05$ was considered significantly.

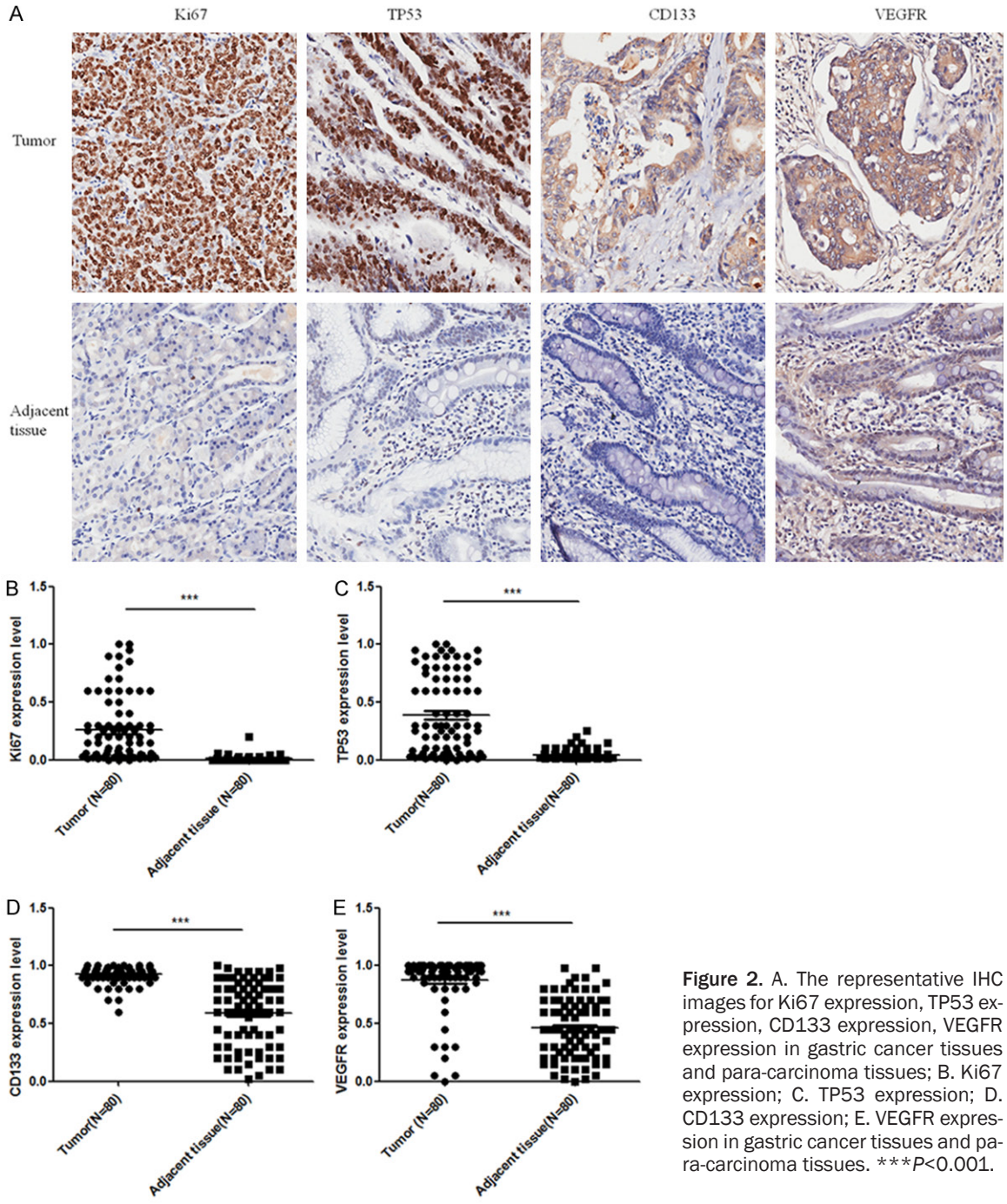

Figure 2. A. The representative IHC images for Ki67 expression, TP53 expression, CD133 expression, VEGFR expression in gastric cancer tissues and para-carcinoma tissues; B. Ki67 expression; C. TP53 expression; D. CD133 expression; E. VEGFR expression in gastric cancer tissues and para-carcinoma tissues. ***P<0.001.

Results

High Rab25 expression in gastric cancer

Rab25 expression was localized in both the cytoplasm and the nuclear of all samples (see **Figure 1A**, **1B**). As the results showed in **Figure 1**, intuitive visualization of high Rab25 expression in both nucleus and cytoplasm was observed in gastric cancer compared to that in para-carcinoma. Further statistical analysis according to Pared T-Test confirmed the aberrant high Rab25 expression in gastric cancer tissues regardless of cytoplasm expression or nucleus expression (cytoplasm: 74.05% ± 24.28% vs 22.76% ± 20.86%, P<0.001; nucleus: 72.44% ± 21.87% vs 41.50% ± 21.66%, P<0.001) (see **Figure 1C**, **1D**). Meanwhile,

Table 2. Correlation between Rab25 cytoplasm/nucleus expression and Ki67/TP53/CD133/VEGFR expression in gastric cancer

		Ki67 expression	TP53 expression	CD133 expression	VEGFR expression
Rab25 cytoplasm expression	Pearson r	0.255*	0.335**	0.491**	0.653**
	P-value	0.011	0.001	0.000	0.000
	Number	98	100	100	100
Rab25 nucleus expression	Pearson r	0.349**	0.330**	0.507**	0.648**
	P-value	0.000	0.001	0.000	0.000
	Number	98	100	100	100

*Correlation is significant at the 0.05 level (2-tailed). **Correlation is significant at the 0.01 level (2-tailed).

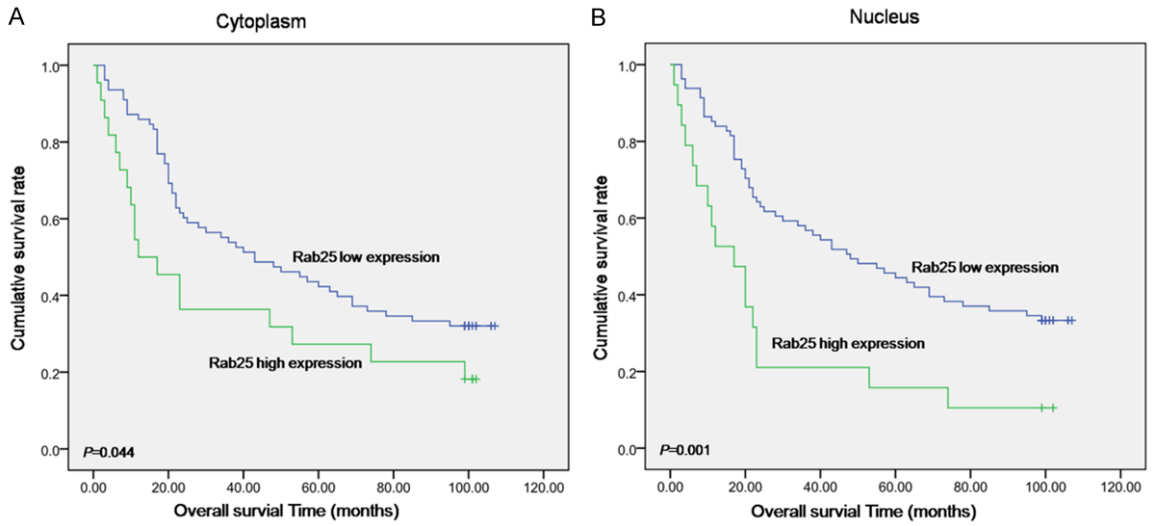

Figure 3. Survival curve dependent on Rab25 cytoplasm/nucleus expression in gastric cancer. *P* values were calculated with log-rank test and $P<0.05$ was considered significantly.

Rab25 cytoplasm expression was positively correlated with Rab25 nucleus expression significantly (r=0.773, $P<0.001$).

Up-regulated Rab25 expression correlated with regional lymphatic metastasis and distant metastasis

As the results summarized in **Table 1**, Rab25 cytoplasm expression was significantly correlated with patients' age (r=0.280, $P=0.005$), distant metastasis (M stage, r=0.287, $P=0.004$) and cTNM stage (r=0.256, $P=0.011$). Similarly, Rab25 nucleus expression had an intense association with M stage (r=0.326, $P=0.001$), cTNM stage (r=0.359, $P<0.001$) as well as regional lymphatic metastasis (N stage, r=0.302, $P=0.003$).

Rab25 associated with Ki67/TP53/CD133/VEGFR in gastric cancer

A series of cancer biomarker expression in gastric cancer (Ki67, TP53, CD133 and VEGFR) were investigated by immunohistochemistry in this study. As the results showed in **Figure 2**, Ki67 (25.68% ± 3.16% vs 1.14% ± 0.28%, **Figure 2B**), TP53 (38.89% ± 3.81% vs 4.55% ± 0.48%, **Figure 2C**), CD133 (93.03% ± 0.84% vs 58.91% ± 3.14%, **Figure 2D**) and VEGFR (87.16% ± 2.67% vs 45.88% ± 2.89%, **Figure 2E**) were all significant evaluated expressed in gastric cancer ($P<0.05$). The relationship between Rab25 expression and Ki67/TP53/CD133/VEGFR expression were further analyzed by Pearson analysis to investigate the potential regulatory molecular mechanism of Rab25 in gastric cancer. The results shown in **Table 2** indicated that Rab25 expression was significantly associated with Ki67 expression (cytoplasm: r=0.255, $P=0.011$; nucleus: r=0.349, $P=0.011$), TP53 expression (cytoplasm: r=0.335, $P=0.001$; nucleus: r=0.330, $P=0.000$), CD133 expression (cytoplasm: r=0.491, $P=0.000$; nucleus: r=0.507, $P=0.000$) and VEGFR expression (cytoplasm: r=0.653, $P=0.000$; nucleus: r=0.648, $P=0.000$).

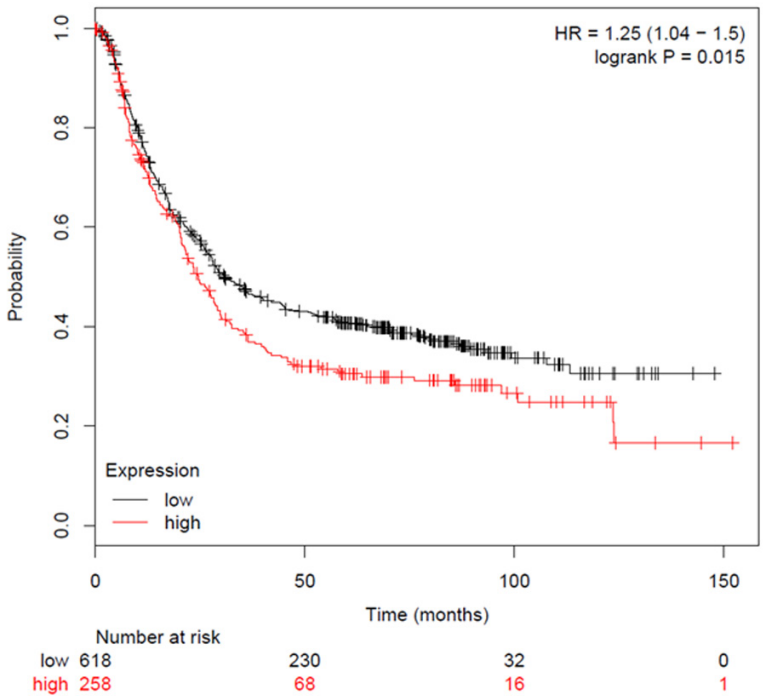

Figure 4. Survival curve dependent on Rab25 expression in gastric cancer by Kaplan-Meier Plotter (http://kmplot.com/analysis/). *P* values were calculated with log-rank test and P<0.05 was considered significantly.

Table 3. Cox regression analysis under inclusion of all potential predict markers in gastric cancer

	P-value	HR	95.0% CI for HR	
			Lower	Upper
Rab25 cytoplasm expression	0.696	0.833	0.333	2.086
Rab25 nucleus expression	0.274	1.663	0.669	4.135
Tumor size	0.266	1.409	0.771	2.576
Histology grade	0.117	1.621	0.887	2.963
T stage	0.007**	2.310	1.255	4.251
N stage	0.105	1.508	0.918	2.476
M stage	0.014*	7.730	1.512	39.530
cTNM stage	0.420	0.634	0.209	1.920

*Correlation is significant at the 0.05 level (2-tailed). **Correlation is significant at the 0.01 level (2-tailed).

High Rab25 expression predicted poor prognosis in patients with gastric cancer

The relationship between Rab25 cytoplasm/nucleus expression and overall survival time of patients with gastric cancer were further analyzed by Kaplan Meier method. As **Figure 3** shown, high Rab25 expression in cytoplasm and nucleus both related with shorter survival time of patients with gastric cancer (18.2% VS 32.1%, *P*=0.044; 10.5% VS 33.3%, *P*=0.001). In a validated cohort of 876 GC patients (Kaplan-Meier Plotter, http://kmplot.com/analysis/), high Rab25 expression was associated with poor prognosis (**Figure 4**). Despite Rab25 expression, there were some clinical characters associated with prognosis, including tumor size, T stage, N stage, M stage and cTNM stage (*P*<0.05, data not show). However COX multivariate survival analysis revealed that neither Rab25 cytoplasm expression nor Rab25 nucleus expression was independent prognosis factor (*P* > 0.05), only T stage and cTNM stage were independent predict markers (*P*<0.05, **Table 3**).

Discussion

The function of Rab25 in cancer was under debate, and gained more attention as a tumor therapy target in recent years. The clinical significance of Rab25, especially the prognostic significance, in gastric cancer had not been fully understood.

According to the immunohistochemistry results, we found out that Rab25 expressed in both cytoplasm and nucleus in all samples and was significantly higher in gastric cancer tissues than that in para-carcinoma tissues. Correlation between Rab25 expression and clinical index indicated that Rab25 expression in nucleus and cytoplasm were positively associated with M stage and cTNM stage (*P*<0.05), suggesting Rab25 might enhance the risk rate of metastasis and thus improve the tumor progression in gastric cancer. Moreover, Rab25 nucleus expression had some link with N stage (*P*<0.05). CAO and colleagues demonstrated high Rab25 expression in gastric cancer associated with some clinical characters (degree of differentiation, TNM stage, N stage

and M stage), in consistent with our observation in this study [9]. However, the regulatory mechanism of Rab25 expression in gastric cancer and the association between Rab25 expression and survival time of patients with gastric cancer was still ambiguity. Our results supplemented the previous results about the Rab25 function in gastric cancer especially the prognostic significance and proposed more possible on regulatory mechanism by analyzing the relationship between Rab25 expression and Ki67/TP53/CD133/VEGFR expression. Survival analysis revealed that high Rab25 nucleus/cytoplasm expression predicted shorter overall survival time of patients with gastric cancer. Neither Rab25 expression in nucleus nor that in cytoplasm was an independent predict marker in gastric cancer, which might attribute to the intense link between Rab25 expression and clinical index. Latter analysis between Rab25 expression and tumor related clinical data further illustrated the tumorigenic mechanism of Rab25 in gastric cancer and the results indicated that Rab25 expression was positively associated with Ki67 expression (a proliferation tumor cell marker), TP53 expression (a cell apoptosis/DNA repaired related biomarker), CD133 (a common cancer stem cell marker) as well as VEGFR ($P<0.05$). Based on these results, we supposed Rab25 to be an oncogene in gastric cancer, and suggested Rab25 might contribute to cancer cell proliferation and apoptosis evading.

The function of Rab25 in tumor progress was quite conflicting. In some types of cancer, down-regulation of Rab25 expression was proved to be favorable prognostic signal, including esophageal carcinoma, colon cancer and head and neck squamous cell carcinoma [3-5, 10]. On the other hand, elevated expression of Rab25 was associated with poor prognosis and thought to play a carcinogenic role in tumor progress, such like ovarian cancer [11-13] andrenal carcinoma [7, 14]. In breast cancer, the function of Rab25 was more complexity, acting as a tumor suppressor in the subgroup of triple negative breast cancer while playing as a oncogene in other subgroups, making the complexity of Rab25 in cancer [15, 16].

To data, the mechanism of Rab25 in cancer has not been fully understood. The most possible mechanism contributed to the oncogenic effects of Rab25 might be the relationship between Rab25 and integrin expression which resulted in enhanced invasion and migration ability of cancer cells [17]. Ki67 was a hallmarker of proliferation cells and usually evaluated in gastric cancer. We hypothesized that Rab25 might promote the proliferation of gastric cancer cells according to regulate Ki67. The immunohistochemistry TP53 was reported to positively associate with malignant features of gastric cancer [18]. Relation with TP53 supported the notion that Rab25 possible inhibit apoptosis of gastric cancer thus functioned as an oncogene. CD133 expression was systematically investigated associating with poor 5-year overall survival in gastric cancer [19]. Similarly, high VEGFR was responsible for poor survival of gastric patients [20]. The positive relationship between Rab25 and Ki67, TP53, VEGFR as well as CD133 expression might support the notion that Rab25 implicated in the carcinogenic progress of gastric cancer. Further study by knocking down or over-expressed *Rab25* gene in gastric cancer lines and normal gastric cell lines was needed to support our notion that Rab25 behaves as an oncogene in gastric cancer.

Moreover, Rab25 was involved in phenylbutyrate treatment-resistant breast cancer [16] and cisplatin resistance ovarian cancer [21], suggesting it play a vital role in drug-resistant of cancer. We further planned to investigate the potential function of Rab25 in drug-resistant of gastric cancer.

In conclusion, our results indicated that Rab25 played a pivotal role in the tumor progression at the tissue protein level and revealed the prognostic significance of Rab25 expression in gastric cancer, suggesting Rab25 to be a potential therapy target of gastric cancer.

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Disclosure of conflict of interest

None.

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