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Original Article

Correlations of Pokemon and Stathmin expression to prognosis of colorectal gastrointestinal stromal tumor

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Abstract: Objective: To investigate the correlations of Pokemon and Stathmin expression to prognosis of colorectal gastrointestinal stromal tumor (CGIST). Methods: Between January 2006 and December 2015, the clinical pathological data and surgical specimens from 56 patients with CGIST, as well as the non-tumor colorectal specimens from 10 patients in the Quzhou People's Hospital were collected and analyzed. The expression of Pokemon and Stathmin in the CGIST tissues was determined with immunohistochemistry. The patients after surgery were followed by phone or outpatient visits and the correlations of Pokemon and Stathmin expression and risk grading in the CGISTs to the rated of disease-free survival (DFS) among patients were analyzed. Results: Among the 56 patients with CGISTs, their sex (P=0.817) and age (P=0.643) were not associated with the DFS rates. The differences in the DFS rates were statistically significant in the four risk subgroups (P=0.002), with the DFS rates lower in the patients with moderate or high risks than in those with low or extremely low risks. The positivity of Pokemon and Stathmin expression increased in the patients with colorectal stromal tumors versus those with normal colorectal tissues (P=0.002, P=0.004), with the positivity of Pokemon and Stathmin expression higher in the patients with moderate or high risks than in those with low or extremely low risks (P=0.000, P=0.000). The DFS rates were significantly different between the patients with positive Pokemon and Stathmin expression and those with negative expression (P=0.005, P=0.008), with the DFS rate of the positive patients lower than that of negative ones. The differences among the three subgroups (0-2, 3-6, 7-9 scores) had statistical significance (P=0.018, P=0.027), whereas the differences between the two subgroups (3-6, 7-9 scores) did not (P=0.123, P=0.435). The positivity of Pokemon and Stathmin expression was negatively related to patients' DFS rate (RR=6.065 and RR=3.823 respectively). Conclusion: Pokemon and Stathmin are factors influencing prognosis of CGISTs.

Keywords: Colorectal gastrointestinal stromal tumor (CGIST), Pokemon, Stathmin, prognostic analysis

Introduction

Gastrointestinal stromal tumor (GIST) is a common mesenchymal tumor in the alimentary tract, mostly arising from Cajal cells in the gastrointestinal tract and primarily from any site in the gastrointestinal tract. GIST arises in stomach (60%-70%), small intestine (25%-35%) and colorectum (5%-10%) [1]. Due to the low incidence of colorectal gastrointestinal stromal tumor (CGIST), there are limited studies and an inadequate understanding of the clinical features and prognostic factors of CGISTs [2]. Few studies and literature reviews for CGIST have been reported in China and other countries. The malignant biological behavior is more obvious in the CGIST than in the GIST in other sites, and prognosis is poor in most patients with CGISTs [3, 4]. Therefore, it is necessary to carry out basic and clinical research on CGIST exploring the mechanisms related to its malignant biological behavior. Studies have shown that Pokemon and Stathmin are two independent factors affecting prognosis of small intestinal stromal tumors [5]. Protein Pokemon is a member of the POK protein family with common structural features, and it can suppress the apoptosis of tumor cells, which is considered as the "master switch" to occurrence and development of tumors [6]. It is over-expressed in many malignant tumor cells and closely related to the biological behavior of tumor cells [7]. Protein Stathmin is a kind of phosphoric acid protein extensively found in the cytoplasm and the latest studies have demonstrated that Stathmin is closely associated with the occurrence,

progression and prognosis of many human tumors [8-10]. The present study was to investigate the relationship between the expressions and disease-free survival (DFS) rates of paients with CGIST by determining the levels of expression of proteins Pokemon and Stathmin in CGIST tissues.

Materials and methods

Specimens and clinical pathological data

We enrolled fifty-six patients with CGIST admitted to the Quzhou People's Hospital from January 2006 to December 2015 in our trial. All the patients underwent complete resection (R0), and received no adjuvant therapy before or after operation. Our study was approved by the Ethics Committee of our hospital and all the subjects provided written informed consent.

Main reagents and instruments

Concentrated DAB reagent kit (Beijing ZSGB Bio, China), Pokemon rabbit anti-human polyclonal antibody and Stathmin rabbit anti-human polyclonal antibody (Beijing Bioss, China); SP immunohistochemical staining kit (Wuhan Boster, China); CKX-41 microscope (Olympus, Japan), microtome (Leica, Germany), transfer liquid gun (Eppendof, Germany), 4°C constant-temperature refrigerator (Siemens, Germany), -20°C constant-temperature refrigerator (Sanyo Electric, Japan), and electronic balance (Ohaus, USA).

SP immunohistochemical staining

Each specimen (the paraffin specimens provided by the Department of Pathology of our hospital) was continuously sliced into three paraffin sections (4 μm thick), one for immunohistochemistry of Stathmin, one for immunohistochemistry of Pokemon, and another one used as negative control with PBS instead of primary antibody. PBS in place of primary antibody was used for blank control. The procedures for SP immunohistochemical staining are as follows: Paraffin sections were deparaffinized in xylene, hydrated in a graded ethanol series, and submitted to antigen retrieval in citrate antigen repair buffer (pH 6.0) at high temperature and under high pressure for 3 min. After natural cooling to room temperature, according to the instructions of the commercial kit, the sections were stained with DAB, counterstained by hematoxylin, differentiated in hydrochloric acid ethanol, dehydrated, remained clear and mounted. Finally, the staining of the sections was observed under microscope. The findings were observed double-blindly, and all the sections were reviewed twice by the associate chief doctors from the Department of Pathology to ensure the reproduction of the findings. With the Sulzers grading method [11], the detected findings were classified into 4 grades in terms of coloring intensity: no positive staining (0 point), light yellow positive particle (1 point), pale brown positive particle (2 points), and brown positive particle (3 points). According to the coloring range, the findings were divided into 4 grades: Grade I, no positive cells (0 point); Grade II, the rates of positivity ≤25% (1 point); Grade III, the rates of positivity varied from 26% to 50% (2 points); and Grade IV, the rates of positivity >51% (3 points). Five high power fields (400×) were observed randomly, and the positivity of 100 cells were calculated for the mean value.

Quantitative expression criteria = coloring intensity * coloring range: 0 point (negative, -), 1-2 points (positive, +), 3-6 points (moderately positive, ++), and 7-9 points (strongly positive, +++). In the findings analysis, ≤2 points is negative; and >2 points is positive.

Follow-ups

All the patients received postoperative follow-ups by phone or outpatient visits once three months, and their recurrence was determined by CT or MRI at a given time [12, 13]. The last follow-up was made on May 30th, 2016, calculated on a monthly basis. Disease free survival (DFS) is defined as the postoperative interval from complete resection of tumor to the recurrence of tumor; for patients without recurrent tumors, DFS is the postoperative interval from complete resection of tumor to the last follow-up; for patients who were lost to follow up, DFS is the postoperative interval from complete resection of tumor to the last successful follow-up.

Outcome measures

This study aimed to investigate the correlations of the positive expression of proteins Pokemon

Table 1. Findings of Pokemon and Stathmin expression

	Case	Pokemo-positive (case)	X^2	P	Stathmin-positive (case)	X^2	P
Risk stratum			22.261	0.000		27.936	0.000
Extremely low	11	3			1		
Low	10	2			2		
Moderate	13	10			11		
High	22	20			19		
Tissue expression			9.434	0.002		8.133	0.004
CGIST	56	35			33		
Normal large intestine tissue	10	1			1		

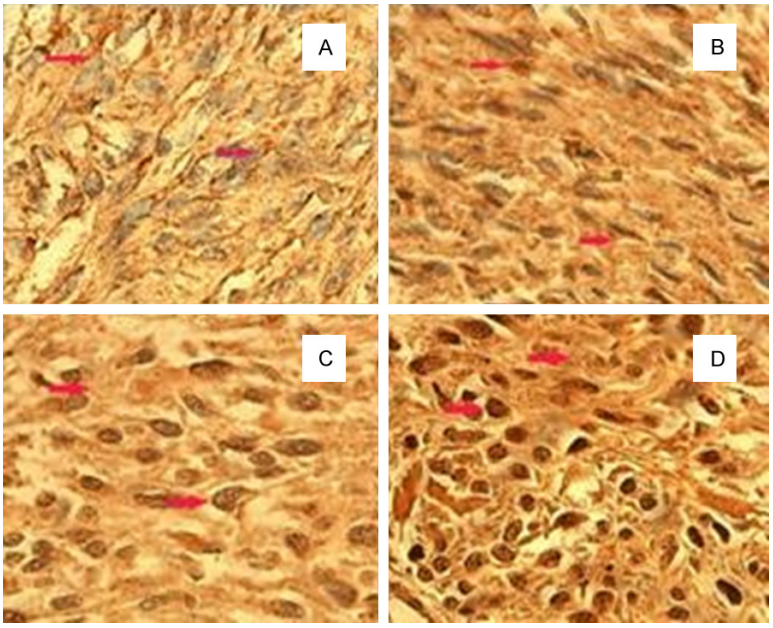

Figure 1. The intracellular localization of Pokemon and Stathmin in the patients with low or high risks. A: Pokemon in the low risk group; B: Stathmin in the low risk group; C: Pokemon in the high risk group; D: Stathmin in the high risk group.

and Stathmin in the tumor tissues of CGIST patients to 3-year and 5-year DFS rates.

Statistical analysis

SPSS 17.0 was used to analyze the experimental data. The X^2 test was applied to analyze the differences between 3-year and 5-year DFS rates, as well as differences between Pokemon and Stathmin expression across groups, whereas variance analysis was used to determine the differences between groups. Survival analysis was calculated by the Kaplan-Meier method, and the difference across the groups was compared by the Log-Rank method. The COX regression model was used for multivariate prognostic analysis. Probability value less than 0.05 was considered statistically significant.

Results

Basic information of patients

A total of 56 patients (25-83 years) were included in this study, including 27 females and 29 males (median age, 55 years; mean age, 54.85± 12.97 yeas). According to the risk grading criteria [14] in *Consensus on diagnosis and treatment of gastrointestinal stromal tumors (GIST) in China (2013 Edition)*, the patients were classified in the risk stratum: extremely low risk (n=11), low risk (n=10), moderate risk (n=13) and high risk (n=22). In our trial, the follow-up period lasted 7-125 months, with median follow-up of 62 months and mean follow-up of 55.6±26.5 months. Two of the 56 CGIST patients were lost to follow-up (one was lost to follow-up at 7 months after the last follow up, the other died from an accident at 11 months).

Comparison of Pokemon and Stathmin expression

The positive expressions of proteins Pokemon and Stathmin were 62.5% and 58.9% respectively in 56 patients with CGIST, and both 10% in 10 cases with normal large intestine tissues.

Table 2. Univariate analysis of prognostic factors

Prognostic factors	Case	3-year DFS (case)	χ^2	*P* value	5-year DFS (case)	χ^2	P
Gender			0.034	0.854		0.054	0.817
Male	29	20			17		
Female	27	18			15		
Age (years)			0.606	0.436		0.215	0.643
<55	26	19			14		
≥55	30	19			18		
Risk stratum			10.001	0.019		15.372	0.002
Extremely low	11	10			10		
Low	10	9			8		
Moderate	13	9			8		
High	22	10			6		
Pokemon expression			11.549	0.001		7.778	0.005
Positive	35	18			15		
Negative	21	20			17		
Pokemon expressionintensity			7.582	0.023		8.008	0.018
0-2 scores	21	18			15		
3-6 scores	12	9			9		
7-9 scores	23	11			8		
Stathmin expression			6.528	0.011		7.108	0.008
Positive	33	18			14		
Negative	23	20			18		
Stathmin expressionintensity			7.220	0.027		7.245	0.027
0-2 scores	23	20			18		
3-6 scores	13	6			5		
7-9 scores	20	12			9		

The differences in the positivity of both Pokemon and Stathmin expression between the CGIST tissues and control tissues showed statistical significance (P=0.002, P=0.004). The positivity of Pokemon expression among the patients with extremely low, low, moderate and high risks (27.3%, 20.0%, 76.9% and 90.9%, respectively) were statistically different (P= 0.000) and the differences between the patients with moderate or high risks and those with extremely low or low risks were statistically significant (P=0.000). The positivity of protein Stathmin in the risk grading (9.1%, 20.0%, 84.6% and 86.4%, respectively) was significantly different (P=0.000) and the differences between the patients with moderate or high risks and those with extremely low or low risks were statistically significant (P=0.000), as shown in **Table 1**.

Immunohistochemical staining showed changes in both quantity and intracellular distribution of proteins Pokemon and Stathmin expression in the patients with low or high risks. **Figure 1A** and **1B** show positive expressions of Pokemon and Stathmin proteins in the cytoplasm of stromal tumor cells in the low risk subgroup, respectively; whereas **Figure 1C** and **1D** show the positive expressions of Pokemon and Stathmin proteins in the cytoplasm and nucleus of stromal tumor cells in the high risk subgroup, respectively.

Findings of follow-ups

Factors of gender (P=0.854, P=0.817) and age (P=0.436, P=0.643) were not associated with 3-year or 5-year DFS rates. The differences in the 3-year and 5-year DFS rates among the patients with extremely low, low, moderate or high risks were statistically significant (P= 0.019, P=0.002), with higher DFS rates in the patients with low or extremely low risks than those with high or moderate risks (P=0.05, P=0.01). The differences in 3-year and 5-year DFS rates between the Pokemon-positive sub-

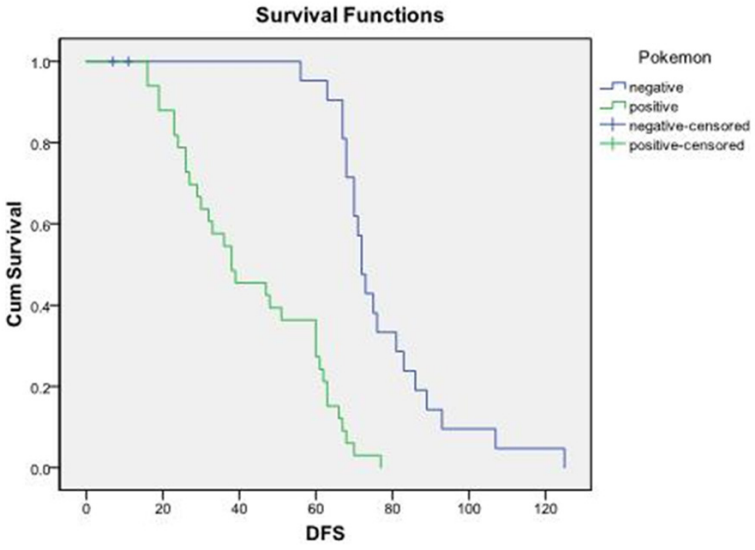

Figure 2. DFS curves of the positive and negative expression of Pokemon.

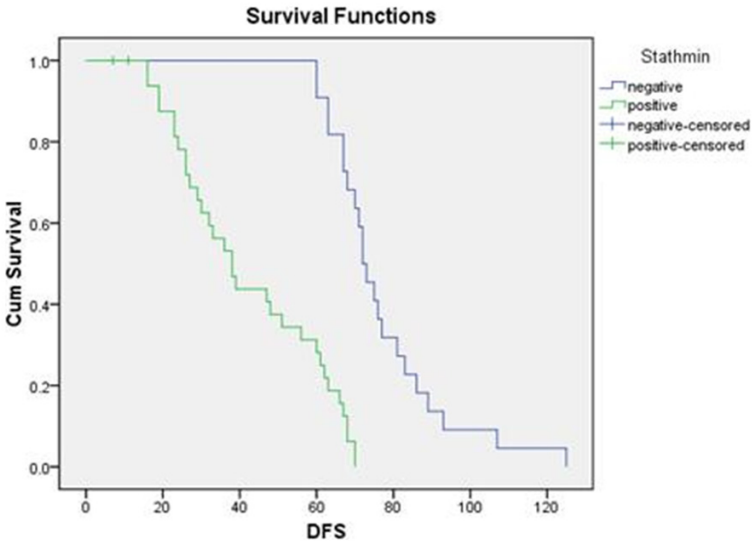

Figure 3. DFS curves of the positive and negative expression of Stathmin.

group and the Pokemon-negative subgroup were statistically significant (P=0.001, P= 0.005), with higher DFS rates in the negative subgroup than in the positive subgroup. The differences in 3-year and 5-year DFS rates between the Stathmin-positive subgroup and the Stathmin-negative subgroup were statistically significant (P=0.011, P=0.008), with higher DFS rates in the negative subgroup than in the positive subgroup. The differences in the 3-year and 5-year DFS rates among the subgroups with (0-2, 3-6, or 7-9 scores) were statistical significant (P=0.027, P=0.027), with higher DFS rates in the subgroup with 0-2 scores than in the subgroups with 3-6 or 7-9 scores. No statistical significance showed in the differences of DFS rates between the patients with 3-6 and those with 7-9 scores regarding Stathmin or Pokemon (P=0.123, P=0.435, respectively), as shown in **Table 2**. The 3-year and 5-year DFS curves concerning proteins Stathmin and Pokemon are shown in **Figures 2** and **3**, respectively. The figures show remarkable differences in the DFS curves between positive and negative expressions of Stathmin and Pokemon detected with the Log-Rank test (P=0.000, P=0.000). The multivariate COX regression analyses showed that risk grading, the expressions of proteins Pokemon and Stathmin were associated with patients' DFS rates; the DFS rates were lower in the patients with moderate or high risks than those with low or extremely low risks; and the DFS rates were lower in the patients with positive Pokemon and Stathmin expression than those with negative expression, as shown in **Table 3**.

Discussion

Gastrointestinal stromal tumor (GIST) was first proposed by Mazur and Clark [15] in 1983. Most of the GISTs experience c-kit or PDGFRA gene mutations, and extensively express CD117 and CD34 [14]. Currently, CD117 and CD34 have become major indicators for diagnosis of GIST. Clinically, accurate judgment of the biological behavior of stromal tumors has been essential for predicting prognosis. However, few studies have reported malignant potential evaluation and prognostic indicators of CGIST.

Table 3. Impact of the DFS time on prognosis of CGIST based on multivariate COX regression analysis

Parameters	Regression coefficients	Wald	P	RR	95% CI
Gender	-0.677	0.311	0.577	0.508	0.047-5.500
Age	-12.699	0.004	0.952	0.000	0.000-1.796
Risk grading	0.947	18.537	0.000	2.577	1.675-3.965
Pokemon	1.803	5.903	0.015	6.065	1.417-25.960
Stathmin	1.341	5.902	0.015	3.823	1.296-11.277

Wu et al [16] and Agaimy A [17] reported that patients with CGIST are prone to recurrence and metastasis, and their DFS durations are shorter than those with GIST. Our study found that the DFS rate of patients with CGIST was correlated to Pokemon and Stathmin expression. The 3-year and 5-year DFS rates of the patients with positive expression of Pokemon and Stathmin significantly decreased. In the risk grading, the 3-year DFS rates were different among the patients. It might be related to the small sample size or to the proportion of the number of cases among the four subgroups (the extremely low risk subgroup, the low risk subgroup, the moderate risk subgroup and the high risk subgroup), with more cases in the extremely low risk subgroup; and it might be also related to the high invasive risks or susceptibility to reoccurrence or metastasis of patients with CGIST. As a result, the risk grading was not completely consistent with the CGIST profile. The efficacy of molecular targeted therapy of imatinib which is a preoperative or postoperative adjuvant therapy for GIST patients, especially for moderate and high risk patients, has been confirmed. In out trial, 46 patients with CGIST in our hospital received no adjuvant therapy before or after operation, mainly due to the following causes: the duration of this trial was long, and Imatinib Mesylate Capsules was approved as a postoperative adjuvant therapy for patients with stromal tumors by FDA in 2008; in addition, in our hospital, few patients had Imatinib Mesylate Capsules before or after operation, which thus would lead to a large bias when included.

Pokemon (known as OCZF or FBI-1) gene, was first reported and confirmed as a new oncogene by American scientists Meada et al [6] in 2005. As a transcriptional repressor, protein Pokemon might be involved in the occurrence and development of tumors in a variety of ways: Davies et al [18] found that Pokemon could aggravate the progression of tumors by co-expression with BCL-6. In recent years, Pokemon has been found to be over-expressed in malignant tumor cells such as cervical cancer, gastric cancer, bladder cancer, colorectal cancer, lung cancer, liver cancer, mammary cancer, and prostatic cancer [6, 19]. Pokemon inhibits ARF-specific (a tumor suppressor gene) transcription, and plays a role in the development modality of the tumors: Pokemon↑→ARF↓→MDM2↑→P53↓ [5]. In our trial, we found that the over-expression of Pokemon was associated with the prognosis of CGIST as its positive expression suggests poor prognosis. However, the differences between the patients with high expression and those with low expression had no statistical significance, which might be related to the above-mentioned mechanisms of Pokemon and its expression, rather than the levels of its expression. There is no denying that the abnormal expression of Pokemon can regulate the functions of several other oncogenes and tumor suppressor genes, leading to CGIST cells in a stage of immune escape, which may be attributed to higher invasive risks, more susceptibility to reoccurrence or metastasis in CGIST cells, and poorer prognosis as compared to the stromal tumors at other sites.

Human protein Stathmin (also known as Oncoprotein 18 or microtubule unstable protein), is involved in the regulation of cell mitosis. In the inter-phase of mitosis, Stathmin is necessary for promoting the disintegration of spindle apparatus and successful completion of mitosis by phosphorylation or dephosphorylation [20]. In recent years, studies in China and other countries have confirmed that Stathmin is over-expressed in many tumors such as prostatic cancer, mammary cancer, ovarian cancer, cervical cancer, liver cancer, lung cancer, and malignant tumors in the digestive system [8-10], and that the 10-year survival rates are significantly higher in the patients with low levels of Stathmin than those with high levels, indicating that Stathmin is an important factor for the prognosis of breast cancer [21]. In our trial, we found that the abnormal expression of Pokemon was associated with the prognosis of CGIST as its positive expression suggests poor

prognosis. However, the differences between the high expression subgroup (7-9 scores) and the low expression subgroup (3-6 scores) had no statistical significance, which might be the causes that the activity of Stathmin depends on not only its levels of protein expression but also its phosphorylation [22]. Therefore, the true activity of Stathmin cannot be showed by its levels of expression alone, and additional studies are required to explore its mechanisms by detecting its phosphorylation. But the abnormal expression of Stathmin will undoubtedly increase its sensitivity to regulation of the signal pathways, and rapidly regulate the balance of microtubule dynamics, which may be associated with the short cell cycle and fast proliferation of CGIST cells.

In summary, the changes in Pokemon and Stathmin expression are associated with prognosis of CGIST, so Pokemon and Stathmin are expected to become new indicators of prognostic prediction of CGIST, as well as new targets of molecular therapy.

Disclosure of conflict of interest

None.

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