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Study on the SPARC Expression and Relationship with Survival in Colorectal Cancer Patients in Han, Buyi and Miao Race

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Abstract

Aims: To investigate the SPARC expression and relationship with survival in Colorectal cancer (CRC) patients in Han, Buyi and Miao race.

Materials & Methods: In our study, SPARC protein expression was detected in 90 available formalin-fixed paraffin-embedded (FFPE) tissues specimens from CRC patients in Han, Buyi and Miao race from the Third Affiliated Hospital of Guizhou Medical University by means of immunohistochemistry. According to the different expression of SPARC, the patients were divided into low expression group (SPARC score of 0+and 1+) and high expression group (SPARC score of 2+ and 3+). The correlations between the two groups in DFS and OS were analyzed, respectively.

Findings: SPARC was mainly expressed in tumor cell cytoplasm and the positive rates of SPARC was 52.2% (47/90). There was no difference in the positive expression rate in the Han, Buyi and Miao race (P =0.87). SPARC expression was related to the pathological type (Adenocarcinoma). There was a marked associations in DFS between the low expression of SPARC group and high expression group (P=0.048, 0.047) in the Han and Miao ethnic. While the same result was no found in the Buyi race (P=0.176). There was no statistical significance in OS between the low expression of SPARC group and high expression group in the Buyi, Miao and Han race, respectively(P= 0.338, 0.424, 0.282).

Conclusion: SPARC was related with DFS in the Miao and Han race, while no correlation in the Buyi race.

Keywords: SPARC; Colorectal Cancer; DFS; OS

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Introduction

Colorectal cancer is one of the third most common malignant tumor, and it is the fourth leading cause of cancer-related deaths in the world [1, 2]. In the past few years, the incidence and mortality rates of CRC continuously rise. SPARC, also known as bone adhesion protein and basal membrane-40 protein, is a member of the extracellular matrix protein family [3]. The expression of SPARC was first identified in bone and endothelial cells played roles in the development and differentiation of chondrocytes and megakaryocytes [4, 5]. SPARC has a wide range of biological effects [6]. SPARC is also expressed in many advanced cancers. Recently, the up-regulated expression of SPARC was associated with gastric cancer, esophageal cancer and CRC [5, 7, 8], and this high levels of SPARC have been shown to be associated with poor prognosis in gastric cancer [8]. SPARC protein directly affects cell adhesion, migration, proliferation, and the formation of blood vessels, plays an important role in the process of the occurrence and development of CRC, and is associated with prognosis in patients [6]. But the different expression level in different race groups have not yet reported. There is no studied about the relationship of SPARC with the prognosis of different race. The aim of this study was to analyze association of SPARC expression in tissue of Han and Buyi and Miao CRC patients with clinical-pathological features, DFS and OS, and to explore new possible prognostic and/or predictive biomarkers for Han, Buyi and Miao CRC patients.

Materials and Methods

The study examined cases from 101 patients diagnosed between 2006 and 2014 in the Third hospital affiliated Guizhou medical university. 11 cases without evaluable tumor tissue were excluded from the analysis. The final database for analysis included 90 cases with histological confirmation. Clinical data of all the cases were reviewed retrospectively from medical records in our hospital. All patients had a minimum 5 years' follow-up records. All the patients underwent operational treatment according to clinical practice guidelines of National Comprehensive Cancer Network (NCCN) of the United States. None of the patients received neo-adjuvant therapy. Statistic and analysis of clinical-pathological parameters, including age at diagnosis, disease stage, tumor size, tumor grade, lymph node status, P53, whether serosa invasion and pathological type, were listed in Table 2.

SPARC expression and evaluation of IHC

All tissues were collected surgically under the supervision of an experienced pathologist. SPARC expression was measured by IHC on FFPE samples. Streptavidin peroxidase (S-P) IHC staining was performed using SPARC antibody of mouse monoclonal (diluted 1/200). The detailed procedures were done as described by Jennbacken [9]. PBS was used to replace the primary antibody in negative controls. According to our data and TMA IHC grading method by Serrero & Ioffe [10] and Pan *et al.* [11], our scoring was semi quantitatively categorized as: ≤5% of tumor cells staining with/without weakly stained was negative (0), followed by a score of 1 (>5% of tumor cells and with weak/focal positive staining or ≤5% of tumor cells with strongly stained), 2 (>5% of tumor cells and with moderate/focal positive staining), 3(>5% of tumor cells and with strong/diffuse positive staining).

Statistical analysis

The correlation between SPARC, clinical-pathological characteristics and survival outcomes was compared by Pearson's X2 test. Examining the significant difference between the groups with T test. Survival analyses, including DFS and OS, were performed with the log rank test and all results were displayed in Kaplan–Meier. DFS was defined as the time interval from date of diagnosis to the time of last disease-free follow-up or at death for those patients who died without a previous recurrence. OS was defined as the time interval from date of diagnosis to time of last follow-up or death [12]. Time to recurrence (local, regional and distant) was censored at time of last disease-free follow-up, and at death for those patients who died without a previous recurrence [12]. Statistical significance was defined as P value<0.05. SPSS17.0 software package was used for all statistical analyses.

Findings

According to the Immunohistochemical results that SPARC is mainly expressed in tumor cell cytoplasm, a few with nuclear expression. SPARC positive test rate was 52.2% (47/90), including 34.1% (16/47) lower expression, 65.9% (31/47) high expression. There was no difference in the positive expression rate in the Han, Buyi and Miao race (P =0.87). (Table 1).

Table 1) SPARC positive rate in the Buyi, Miao and Han race

Race	SPARC		Whole SPARC positive rate (%)	P-value
	positive	Rate (%)		
Han	16	53.3	52.2	0.87
Buyi	15	50.0		
Miao	16	53.3		

To evaluate SPARC prognostic significance, We divided the cases into two groups, one is the high SPARC expression group(SPARC score of 2+and 3+), the other one is low SPARC expression group (SPARC score of 0, and 1+).We analyzed SPARC different expression in relation with DFS and OS in CRC patients. There was a marked associations with DFS in Han and Miao race (p =0.048, 0.047) (Figure 1). While the same result was no found in Buyi race (p=0.176) (Figure 1). But no significant difference was found in OS. OS Function curves showed no separation in Han, Miao and Buyi race (P= 0.338, 0.424, 0.282) (Figure 2).

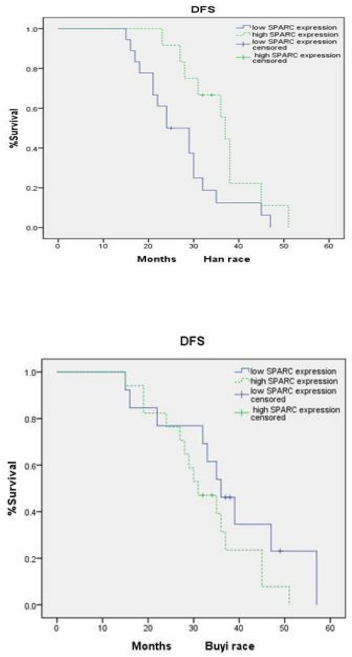

Figure 1) Kaplan-Meier estimates for DFS by high expression group and low expression group in Han, Miao and Buyi race.

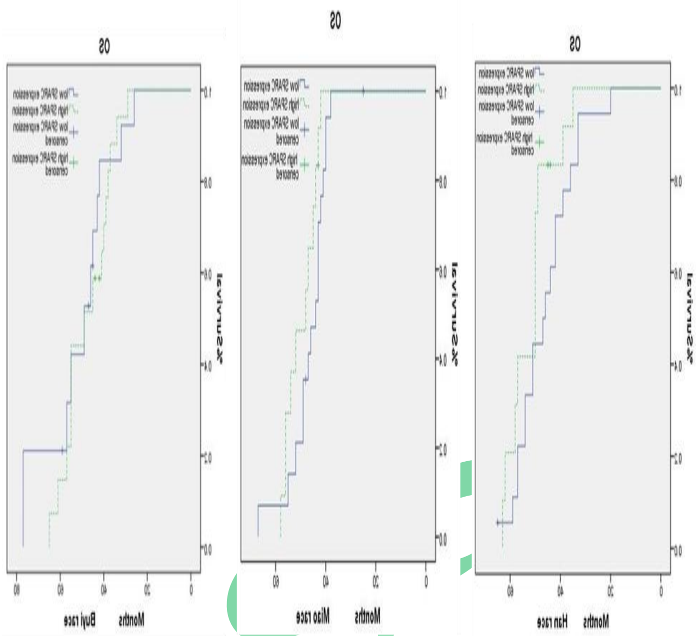

Figure 2) Kaplan-Meier estimates for OS by high expression group and low expression group in Han, Miao and Buyi race.

Table 2) Clinicopathological characteristics of patients

Parameter	Number(n)	Subgroup cut-offs	SPARC positive		SPARC negative		*P*-value
			Number(n)	%	Number(n)	%	
Age	90						
	55	X>35	29	32.2	26	28.9	0.49
	35	X≤35	18	20.0	17	18.9	
TNM staging	90						
	9	I(1)	4	4.4	5	5.6	0.57
	35	II(2)	19	21.1	16	17.8	0.62
	46	III (3)	22	24.4	24	26.7	0.71
P53	90						
	53	Mutated No-mutated	35	38.9	18	20.0	0.81
	37		25	27.8	12	13.3	0.50
Node	90						
	82	+	42	46.7	40	44.44.4	0.68
	8	_	4	4.4	4		0.50
Grade	90						
	36	Low/Mod	20	22.2	16	17.8	0.71
	28	High	13	14.4	15	16.6	0.87
Pathological type	90						
	69	Adenocarcinoma	40	44.4	29	32.2	0.04
	21	No-Adenocarcinoma	10	11.1	11	12.2	0.06
invade serosa	90						
	77	+	39	43.3	38	42.2	0.82
	13	-	7	7.8	6	6.7	0.70

Discussion

Colorectal cancer is one of the most common malignant tumor. Many factors are involved in the invasion and metastasis of malignant tumor development. And studies various adhesion factors, such as hydrolytic enzymes, growth factors and the matrix protein, are associated with invasion and metastasis of tumor. SPARC is a kind of calcium binding protein. Alexandre & Susan [13], summarized the main function of SPARC. SPARC could destroy the cell adhesion, promote cell deformation, inhibition of cell cycle, regulate cell differentiation, inhibit cell response to some growth factors, adjust the extracellular matrix and matrix metalloproteinase and affect the new angiogenesis.

Several studies show that SPARC is associated with the prognosis of CRC. Yang *et al.* [14] analyzed that SPARC in the lower expression of tumor cells and associated with poor prognosis in 292 cases of primary CRC patients by the 5-year survival rate. While Liang *et al.* [15] found SPARC expression in CRC tumor stroma is associated with the clinical pathological factors, and survival analysis showed that the low SPARC expression in tumor stroma is the cause of the prognosis. In our study that positive SPARC test rate was 52.2% (47/90), including 34.1% (16/47) lower expression, 65.9% (31/47) high expression. There was no difference in the positive expression rate in the Han, Buyi and Miao race, (P = 0.87).SPARC expression was related to the pathological type (Adenocarcinoma) and was no significant correlations with age, nuclear grade, nodal involvement, TNM stage, serosa invasion and P53. There was a marked associations in DFS between the low expression of SPARC group and high expression group (P = 0.048, 0.047) in the Han and

Miaorace. While the same result was no found in the Buyi race (P=0.176). There was no statistical significance in OS between the low expression of SPARC group and high expression group in the Buyi, Miao and Han race, respectively(P= 0.338, 0.424, 0.282). In short, we have demonstrated that SPARC is almost the same expression in CRC patients in Han, buyi and Miao race by immunostaining and SPARC may be viewed as an prognostic factor of DFS in Han and Miao race, but not in Buyi race. We suggest that SPARC could be a promising prognostic biomarker in CRC patients in Han and Miao race for cancer prognostic, as well as be a possible target for the treatment of these patients.

Conclusion

None.

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