SPANDIDOS PUBLICATIONS

ONCOLOGY LETTERS 15: 4604-4610, 2018

Low scavenger receptor class B type I expression is associated with gastric adenocarcinoma tumor aggressiveness

XINGWEN WANG[1], CHANGSHUN WU[2], BAOYING YUAN[1], DAN WANG[3], HUILING LIU[1], HONG FENG[1] and SHUI SUN[2]

[1]Cancer Center; Departments of [2]Bone and Joint Surgery and [3]Central Laboratory, Shandong Provincial Hospital Affiliated to Shandong University, Shandong University, Jinan, Shandong 250021, P.R. China

Received July 15, 2016; Accepted December 20, 2017

DOI: 10.3892/ol.2018.7889

Abstract. Scavenger receptor class B type I (SR-BI), a well-documented high-density lipoprotein receptor, has been implicated in the development and progression of human cancer. However, little is known regarding the expression profile and clinical value of SR-BI in gastric adenocarcinoma. In the present study immunohistochemistry analysis was performed on a well-annotated gastric adenocarcinoma tissue microarray to investigate the association between SR-BI expression and clinicopathological parameters or patient outcome. The results revealed that SR-BI expression was detected in 69% of the 84 gastric adenocarcinomas. Moreover, a significant association was observed between low SR-BI expression and poor histological grade, higher Tumor-Node-Metastasis T stage, higher N stage and diffuse type carcinoma. Low SR-BI expression was also significantly associated with a shorter overall survival time in patients with gastric adenocarcinoma, although it was not an independent prognostic factor. Overall, the results of the present study demonstrated that SR-BI was possibly involved in gastric carcinogenesis and could be used as a biomarker to predict malignancy of gastric adenocarcinoma.

Introduction

Gastric adenocarcinoma is a major contributor to the global health burden, ranking as the fifth most common type of malignancy worldwide (1). Gastric adenocarcinoma is the second-leading cause of cancer death owing to its poor prognosis (2). The identification of novel biomarkers with potential prognostic value would aid the assessment of patient prognosis and the selection of therapeutic treatments for individual patients with gastric adenocarcinoma.

Scavenger receptor class B type I (SR-BI) is a well-documented high-density lipoprotein (HDL) receptor, which is most abundantly expressed in liver and the steroidogenic tissues, including the ovaries, testes and adrenal glands (3). SR-BI mediates the selective uptake of HDL cholesteryl esters and the bidirectional transfer of unesterified cholesterol between cells and HDL. In addition, SR-BI serves a role in sepsis, adaptive immune and hepatitis C virus entry (4-6). It is becoming increasingly apparent that SR-BI serves a role in cancer development (7,8). Pronounced expression of SR-BI was observed in a variety of carcinomas, including hepatoma, prostate, breast, colorectal, pancreatic, ovarian, and nasopharyngeal cancer (9-12). Moreover, SR-BI has been demonstrated to exert a profound influence on the proliferation, migration and invasion of breast and prostate cancer cells (7,8). In human stomach, Lobo *et al* (13) reported that SR-BI was not detected in epithelial, parietal, mucous and endocrinal cells. However, to the best of our knowledge, the status of SR-BI expression in gastric adenocarcinoma and its clinical significance have not been reported to date.

The present study evaluated the expression of SR-BI using a high-throughput tissue microarray containing 90 cases of gastric carcinomas, with the aim of investigating its association with clinicopathological variables and patient outcome.

Materials and methods

Human gastric adenocarcinoma tissue microarray. The commercial gastric adenocarcinoma tissue microarray (cat. no. HStm-Ade180Sur-06; Shanghai Outdo Biotech Co., Ltd., Shanghai, China) contained samples from 90 individual cases, with each adjacent non-cancerous tissue placed next to its matched cancer tissue. Of the 90 invasive carcinoma samples used to construct the tissue microarray, 84 were available for evaluation, excluding the uninformative tissue microarray cores that were either lost or fragmented during the immunohistochemical procedure. The clinical characteristics of the 84 patients are listed in Table I. The cohort included

Correspondence to: Dr Hong Feng, Cancer Center, Shandong Provincial Hospital Affiliated to Shandong University, 324 Jingwu Weiqi Road, Jinan, Shandong 250021, P.R. China
E-mail: 18264632717@163.com

Dr Shui Sun, Department of Bone and Joint Surgery, Shandong Provincial Hospital Affiliated to Shandong University, 324 Jingwu Weiqi Road, Jinan, Shandong 250021, P.R. China
E-mail: sunshui1268@126.com

Key words: gastric adenocarcinoma, scavenger receptor class B type I, prognosis, immunohistochemistry, aggressiveness

50 male and 34 female patients, with a median age of 63 years (range 28-88 years) at the time of surgery. These specimens were collected from patients who underwent primary surgical resection between August 2008 and March 2009. No chemotherapy or radiotherapy was conducted in these patients prior to surgery. All the gastric adenocarcinoma patients included had well-documented clinicopathological data and follow-up information. The histological grade was determined according to the World Health Organization classification criteria (14). The histotype was based on the criteria of Lauren's classification (15). The pathological Tumor-Node-Metastasis (pTNM) stage was assessed according to the 7th Edition of the staging system set out by American Joint Committee on Cancer (AJCC) (16). Overall survival (OS) time, defined as the time from the date of surgery to death or last follow-up, was used as a measure of prognosis. All patients were followed-up until death or until September 2014 with a median of 24 months (range, 1-73 months). The research was approved by the Ethical Committee of Shandong Provincial Hospital affiliated to Shandong University (Jinan, China).

Immunohistochemistry. The tissue microarray slide was deparaffinized and rehydrated in graded solutions of ethanol (100, 95, 80, and 70%) and distilled water for 5 min in room temperature. For antigen retrieval, the slide was immersed in 10 mM citrate buffer (pH 6) and boiled for 5 min in a pressure cooker. Following incubation with 3% hydrogen peroxide for 15 min at room temperature to eliminate endogenous peroxidase activity, the slide was incubated with normal goat serum (dilution 1:10; cat. no. C-0005; Jiangxi Haoran Bio-Pharma Co., Ltd., Shanghai, China) for 20 min at 37˚C to reduce non-specific staining. The slide was then incubated with the monoclonal rabbit anti-human SR-BI antibody (dilution 1:100; cat. no. EP1556Y; Abcam, Cambridge, UK) overnight at 4˚C in a moist chamber. The following day, the slide was washed three times in PBS and incubated with a horseradish peroxidase-conjugated goat anti-rabbit antibody (dilution 1:1; cat. no. SP-9001; Zhongshan Biotechnology Co., Beijing, China) for 30 min at room temperature. Bound antibodies were visualized using diaminobenzidine prior to counterstaining with hematoxylin for 5 min at room temperature. Negative control was included by replacement of the primary antibody with phosphate-buffered saline. The specificity of the rabbit anti-human SR-BI antibody was confirmed by Bogan *et al* (17) with the synthetic peptide used to produce the antibody as a control. The slides were then visualized using a bright field microscope (Olympus CX31; Olympus Corporation, Tokyo, Japan) under x40 or x200 magnification.

Immunohistochemical evaluation. Immunohistochemical staining for SR-BI expression was evaluated and scored independently by two pathologists blinded to the clinicopathological characteristics and outcomes of the patients. The immunostaining scores were based on the staining intensity and the proportion of stained cells. Staining intensity was scored as follows: 0, negative; 1, weak; 2, moderate; and 3 strong. The percentage of positive-stained cells was scored as follows: 0, 0%; 1, <10%; 2, 10-50%; 3, 51-80%; and 4, >80%. For each case, a modified immunoreactive score was obtained by multiplying the intensity and the percentage scores (18), with scores ranging from 0 to 12. Tumor specimens with a final score of 0-4 were considered to exhibit low expression and those with a final score of 6-12 were regarded to exhibit high expression. Discrepancies between the pathologists were resolved by consensus following discussion.

Table I. Clinicopathological characteristics of the patient cohort (n=84).

Variable	Patients, % (n)
Age, years	
<60	38 (32)
≥60	62 (52)
Gender	
Female	40 (34)
Male	60 (50)
Tumor size, cm	
<4	26 (22)
≥4	74 (62)
Grade	
Well/moderate	23 (19)
Poor	77 (65)
Lauren type	
Intestinal type	57 (48)
Diffuse type	43 (36)
Tumor location	
Cardia	11 (9)
Body/antrum	89 (75)
Lymphatic invasion	
Negative	73 (61)
Positive	27 (23)
pTNM stage	
I-II	39 (33)
III-IV	61 (51)
T classification	
T1-T2	14 (12)
T3-T4	86 (72)
N classification	
N0	26 (22)
N1-N3	74 (62)
Distant metastasis	
M0	95 (80)
M1	5 (4)

pTNM, pathological Tumor-Node-Metastasis.

Statistical analysis. All statistical analyses were performed using SPSS software (version 19; IBM Corp., Armonk, NY, USA). The χ^2 test or Fisher's exact test was used to analyze the associations between SR-BI expression and clinicopathological factors. Survival analysis was performed using the Kaplan-Meier method, with the log-rank test used to compare

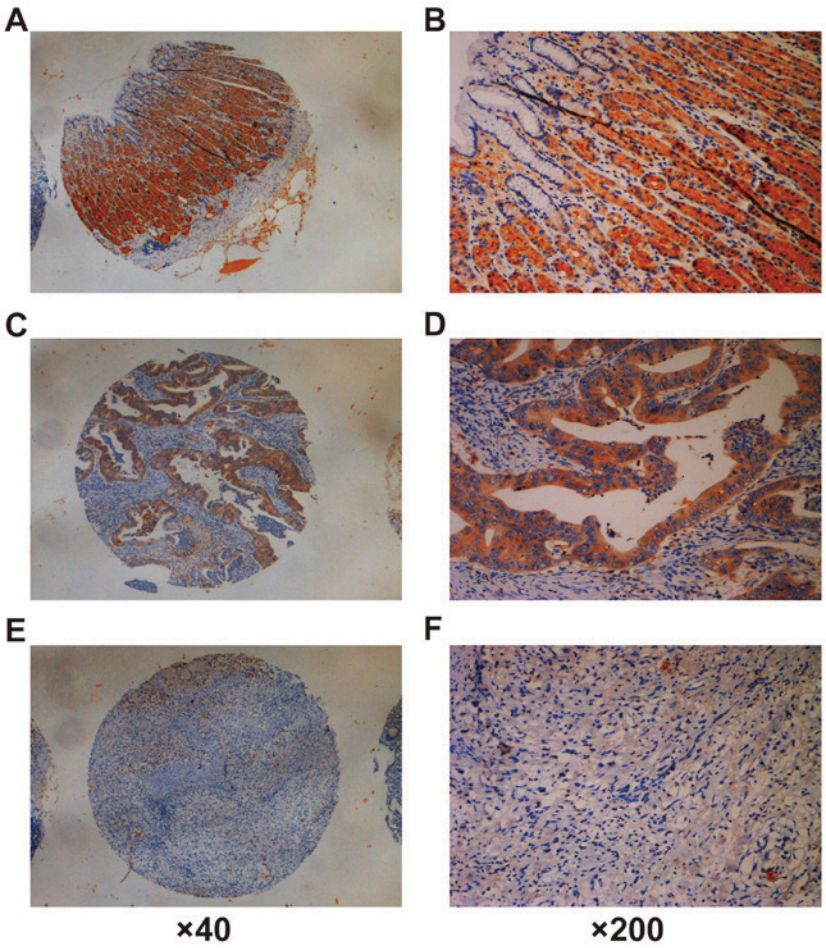

Figure 1. Immunohistochemical staining of SR-BI in adjacent non-cancerous tissue and gastric adenocarcinoma tissues. (A and B) In gastric non-cancerous tissue, high SR-BI staining was observed in the cells of the fundic glands, but was barely detecTable in the surface epithelial cells adjacent to the gastric lumen. (C and D) Representative images show that high SR-BI expression was detected in a Lauren intestinal type carcinoma case (intensity score, 2; final score, 8). (E and F) Representative images depicting that low SR-BI expression was detected in a Lauren diffuse type of gastric carcinoma case (intensity score, 0; final score, 0). (A, C and E, x40 magnification; B, D and F, x200 magnification). SR-BI, Scavenger receptor class B type I.

between different patient groups. Multivariate analysis was performed using a Cox proportional hazard model to evaluate the effect of clinicopathological variables and SR-BI expression on OS rate [hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated]. All statistical tests were two-sided; $P<0.05$ was considered to indicate a statistically significant difference.

Results

Clinicopathological features of the specimens. Tumor size was determined on the basis of the maximum diameter of the primary lesions. There were 22 cases with tumors <4 cm and 62 with tumors ≥4 cm. A total of 65 patients had poorly differentiated tumors and 19 patients had moderately or well differentiated tumors. The samples included 48 intestinal-type carcinomas and 36 diffuse-type carcinomas, according to Lauren's classification. The tumor location distribution was 11% cardia and 89% non-cardia. Lymphatic invasion was found in 23 cases. According to the pTNM classification system, 8 cases were categorized as stage I, 25 cases as stage II, 47 cases as stage III, and 4 cases as stage IV. A total of 62 patients had lymph node metastasis and 4 patients had distant metastasis.

Associations between SR-BI expression and clinicopathological parameters. In gastric non-cancerous tissue, strong SR-BI staining was observed in the cells of the fundic glands, but was barely detectable in the surface epithelial cells adjacent to the gastric lumen (Fig. 1A and B). Expression of SR-BI was observed at membranous and cytoplasmic localizations. Among 84 cases of gastric adenocarcinoma, expression of SR-BI was observed in 58 (69%) cases. More specifically, 24 (28.6%) samples exhibited high SR-BI expression (range 6-10, average 8.2), whereas the remaining 60 cases (71.4%) exhibited low SR-BI expression (range 0-4, average 1.8). No staining of SR-BI was observed in the negative control slide. The association between SR-BI expression and clinicopathological features of gastric adenocarcinomas was analyzed. As summarized in Table II, the proportion of carcinomas exhibiting high SR-BI protein expression of was 10/19 (52.6%) in well-and moderately-differentiated cancer samples and 14/65 (21.5%) in poorly-differentiated carcinoma samples, and a significant inverse association was found between SR-BI expression and histological grade ($P=0.008$). Similarly, high SR-BI expression was observed more frequently in the Lauren intestinal type (Fig. 1C and D) than in the diffuse type of gastric carcinomas (Fig. 1E and F)

Table II. Association of SR-BI protein expression with clinicopathological characteristics in patients with gastric cancer (n=84).

Variable	Patients, n	SR-BI expression, % (n)		P-value
		Low	High	
Total	84	71 (60)	29 (24)	
Age, years				0.118
<60	32	43 (26)	25 (6)	
≥60	52	57 (34)	75 (18)	
Gender				0.527
Female	34	38 (23)	46 (11)	
Male	50	62 (37)	54 (13)	
Tumor size, cm				0.346
<4	22	23 (14)	33 (8)	
≥4	62	77 (46)	67 (16)	
Grade				0.008
Well/moderate	19	15 (9)	42 (10)	
Poor	65	85 (51)	58 (14)	
Lauren type				<0.001
Intestinal type	48	40 (24)	100 (24)	
Diffuse type	36	6 (36)	0 (0)	
Tumor location				0.435
Cardia	9	13 (8)	4 (1)	
Body/antrum	75	87 (52)	96 (23)	
Lymphatic invasion				0.757
Negative	61	72 (43)	75 (18)	
Positive	23	28 (17)	25 (6)	
pTNM stage				0.203
I-II	33	35 (21)	50 (12)	
III-IV	51	65 (39)	50 (12)	
T classification				<0.001
T1-T2	12	5 (3)	37 (9)	
T3-T4	72	95 (57)	62 (15)	
N classification				0.010
N0	22	18 (11)	46 (11)	
N1-N3	62	82 (49)	54 (13)	
Distant metastasis				1.000
M0	80	9% (57)	96 (23)	
M1	4	5 (3)	4 (1)	

SR-BI, Scavenger receptor class B type I; pTNM, pathological Tumor-Node-Metastasis.

according to the Lauren classification (P<0.001). In addition, SR-BI expression was significantly associated with T stage (P<0.001) and N stage (P=0.010). However, no significant association was observed between SR-BI expression and age, gender, tumor size, tumor location, lymphatic invasion, distant metastasis or pTNM stage.

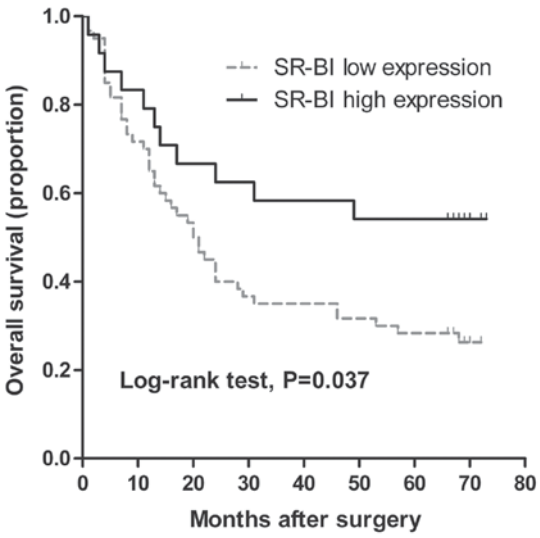

Figure 2. Kaplan-Meier curves showed that patients with low SR-BI expression had poor overall survival compared with patients with high SR-BI expression (P=0.037). SR-BI, Scavenger receptor class B type I.

SR-BI expression and patient outcome. The association between SR-BI expression and overall survival was assessed in gastric adenocarcinoma patients using univariate analysis. As shown in Fig. 2, Kaplan-Meier survival curves indicated that patients with low SR-BI expression had a significantly shorter OS time compared with patients with high SR-BI expression (P=0.037 by log-rank test). The 5-year survival rate for gastric adenocarcinoma patients with low SR-BI expression was 28%, compared with 54% for the group with SR-BI high expression. Additionally, tumor size, grade, Lauren type, pTNM stage, T stage, N stage, distant metastasis and lymphatic invasion were also associated with the risk of death (Table III). No prognostic associations were observed with age, gender, or tumor location. Furthermore, multivariate analysis using the Cox regression model revealed that T stage, N stage and lymphatic invasion were independently and significantly associated with survival (P=0.035, P=0.002 and P=0.013, respectively; Table IV). However, SR-BI expression was not an independent prognostic factor.

Discussion

Multiple studies have found that SR-BI is implicated in the regulation of diverse tumor cell biology, including tumor cell proliferation, apoptosis, migration and invasion (7,8). The present study analyzed the expression of SR-BI in multiple gastric adenocarcinoma specimens and found that SR-BI immunoreactivity was present in 69% of cases. Specifically, high SR-BI expression was detected in 28.6% of patients, all of whom had intestinal type disease. In addition, low SR-BI expression was significantly associated with clinicopathological parameters indicative of a more aggressive tumor type, including poor histological grade, higher T stage, higher N stage and diffuse type carcinoma. Patients with low SR-BI expression had poorer prognoses in the patient cohort of the present study.

The data from the normal gastric tissue were in line with the previous paper by Lobo *et al* (13), which demonstrated that

Table III. Univariate survival analysis of 84 gastric cancer patients.

Variable	Estimated 5-year OS rate, %	P-value
Age, years		0.167
<60	25	
≥60	42	
Gender		0.171
Female	29	
Male	40	
Tumor size, cm		0.028
<4	55	
≥4	29	
Grade		0.021
Well/moderate	63	
Poor	28	
Lauren type		0.027
Intestinal type	46	
Diffuse type	22	
Tumor location		0.546
Cardia	22	
Body/antrum	37	
Lymphatic invasion		<0.001
Negative	48	
Positive	4	
pTNM stage		<0.001
I-II	82	
III-IV	6	
T stage		0.001
T1-T2	83	
T3-T4	28	
N stage		<0.001
N0	86	
N1-N3	18	
Distant metastasis		0.009
M0	38	
M1	0	
SR-BI expression		0.037
Low	28	
High	54	

SR-BI, Scavenger receptor class B type I; pTNM, pathological Tumor-Node-Metastasis.

SR-BI was predominantly detected in the majority of cells in the fundic gland, but not in the normal gastric mucosa. As SR-BI was not detected in epithelial, parietal, mucous or endocrinal cells (13), we hypothesized that SR-BI might be mainly located in chief cells. Further immunofluorescence staining in future studies is warranted to determine the exact cellular location of SR-BI.

Table IV. Multivariate survival results.

	Overall survival		
Variable	HR	95% CI	P-value
T stage	4.688	1.115-19.710	0.035
N stage	5.400	1.869-15.605	0.002
Lymphatic invasion	2.080	1.165-3.711	0.013

HR, hazard ratio; CI, confidence interval; T, Tumor; N, Node.

Gastric adenocarcinoma is a heterogeneous disease that can be classified into two major histological subtypes based on Lauren's criteria: Intestinal type and diffuse type adenocarcinomas. The intestinal type gastric adenocarcinoma is possibly preceded by precancerous changes in the gastric mucosa, including chronic atrophic gastritis, intestinal metaplasia and dysplasia (14,19). The progression of gastric fundic gland polyps and the transdifferentiation of chief cells was reported to be involved in the initiation of intestinal metaplasia (19); however, diffuse-type gastric carcinoma seems to be less associated with environmental influences and precancerous changes (19), and it is believed to originate from mucous neck cells or stem cells (20). Evidence indicates that the molecular profiles of these subtypes are distinct (21-24). In the present study, marked differences in SR-BI expression between the intestinal type and diffuse type supported the notion that distinct precursors and pathways led to the oncogenesis of the two types of gastric adenocarcinoma.

Epidemiological studies have provided evidence indicating the presence of strong associations between serum lipid profiles and gastric adenocarcinoma (25,26). Considerable alterations have been documented regarding serum total cholesterol, triglyceride, HDL cholesterol and low-density lipoprotein cholesterol levels in patients with gastric adenocarcinoma compared with those in non-cancer subjects (25). In particular, low serum HDL-cholesterol was reported to be a negative prognostic factor for gastric adenocarcinoma patients (26). Low-density lipoprotein receptor (LDLR) levels in diffuse type gastric adenocarcinoma were significantly lower than those in normal mucosa, but there was no significant difference between intestinal-type gastric adenocarcinoma and normal mucosa (27). Caveolin-1 is a scaffolding protein that binds to cholesterol and is involved in intracellular cholesterol trafficking. Barresi *et al* (28) reported that caveolin-1 expression was significantly higher in intestinal-type gastric adenocarcinoma than in the diffuse type. Similar to LDLR and caveolin-1, SR-BI expression in intestinal-type cancer was also higher than that in diffuse-type cancer in the present study. The differences in the aforementioned cholesterol-trafficking proteins between the two histological types indicated the presence of distinct cholesterol metabolism in these adenocarcinomas, which warrants further investigation.

Previous studies have shown that certain HDL-cholesterol-elevating drugs may regulate SR-BI protein expression. Statins increase SR-BI expression in several cell types, including macrophages (29), adipocytes (30), keratinocytes (31), and endothelial cells (32). Fibrates can affect HDL metabolism in

mice by downregulating hepatic SR-BI protein levels (33,34). The commercial tissue microarray did not provide detailed information regarding the plasma lipoprotein profiles or drug treatments (e.g. statins and fibrates) of patients, meaning that the possible influence of these factors on SR-BI expression in gastric tissues could not be evaluated. Further study is therefore required to answer these questions.

Several studies have reported the role of SR-BI in diverse solid tumors (7,35,36). For instance, SR-BI was shown to mediate the proliferative and anti-apoptotic features of HDL in MCF-7 breast cancer cells through modulation of cholesterol metabolism (7,8). Twiddy *et al* (36) found that SR-BI downregulation caused a significant reduction in prostate-specific antigen production and decreased the viability of prostate cancer cell lines *in vitro*. Previous studies revealed that SR-BI was associated with more aggressive cancer phenotypes and could serve a tumor-promoting function in breast and prostate cancer (35,37). However, in gastric adenocarcinoma, the role of SR-BI appeared to be different. In contrast to the findings of those prior studies, low SR-BI expression was associated with the more aggressive phenotype contrarily. Therefore, the role of SR-BI may be complex and tissue-dependent, and it may have versatile functions in different types of cancer. In gastric fundic gland cells, SR-BI may be involved in the active exocytosis of pepsinogen, as a high degree of membrane cholesterol metabolism is required in this process (38), whereas in gastric adenocarcinoma, the pepsin-secreting function of cells was diminished (38). We hypothesized that this may be the reason for the downregulation of SR-BI in gastric adenocarcinoma.

Despite the strong association between SR-BI expression and multiple types of cancer, reports linking SR-BI to the clinical outcome of cancer patients are limited. The results of a previous study revealed that high SR-BI expression was an independent factor predictive of poor prognosis for patients with breast cancer (35). Schörghofer *et al* (37) reported that high SR-BI expression was associated with shorter disease-free survival times in prostate cancer. On the contrary, in gastric adenocarcinoma, patients with low SR-BI expression had significantly poorer prognosis than patients with high SR-BI expression, indicating that different mechanisms were involved.

In summary, the results of the present study demonstrated that low SR-BI expression was associated with malignancy and unfavorable prognosis in patients with gastric adenocarcinoma. Further research is therefore warranted to clarify the role of SR-BI in gastric adenocarcinoma.

Acknowledgements

This study was supported by grants from the National Natural Science Foundation of China (nos. 81201865, 81202307 and 81271966), and Shandong Science and Technology Development Planning (nos. 2015GSF118169 and 2012G0021822) and Shandong Natural Science Foundation (no. ZR2017QH004).

References

1. McLean MH and El-Omar EM: Genetics of gastric cancer. Nat Rev Gastroenterol Hepatol 11: 664-674, 2014.
2. Rahman R, Asombang AW and Ibdah JA: Characteristics of gastric cancer in Asia. World J Gastroenterol 20: 4483-4490, 2014.
3. Acton S, Rigotti A, Landschulz KT, Xu S, Hobbs HH and Krieger M: Identification of scavenger receptor SR-BI as a high density lipoprotein receptor. Science 271: 518-520, 1996.
4. Guo L, Song Z, Li M, Wu Q, Wang D, Feng H, Bernard P, Daugherty A, Huang B and Li XA: Scavenger receptor BI protects against septic death through its role in modulating inflammatory response. J Biol Chem 284: 19826-19834, 2009.
5. Li Y, Kakinami C, Li Q, Yang B and Li H: Human apolipoprotein A-I is associated with dengue virus and enhances virus infection through SR-BI. PLoS One 8: e70390, 2013.
6. Feng H, Guo L, Wang D, Gao H, Hou G, Zheng Z, Ai J, Foreman O, Daugherty A and Li XA: Deficiency of scavenger receptor BI leads to impaired lymphocyte homeostasis and autoimmune disorders in mice. Arterioscler Thromb Vasc Biol 31: 2543-2551, 2011.
7. Cao WM, Murao K, Imachi H, Yu X, Abe H, Yamauchi A, Niimi M, Miyauchi A, Wong NC and Ishida T: A mutant high-density lipoprotein receptor inhibits proliferation of human breast cancer cells. Cancer Res 64: 1515-1521, 2004.
8. Danilo C, Gutierrez-Pajares JL, Mainieri MA, Mercier I, Lisanti MP and Frank PG: Scavenger receptor class B type I regulates cellular cholesterol metabolism and cell signaling associated with breast cancer development. Breast Cancer Res 15: R87, 2013.
9. Wadsack C, Hirschmugl B, Hammer A, Levak-Frank S, Kozarsky KF, Sattler W and Malle E: Scavenger receptor class B, type I on non-malignant and malignant human epithelial cells mediates cholesteryl ester-uptake from high density lipoproteins. Int J Biochem Cell Biol 35: 441-454, 2003.
10. Leon CG, Locke JA, Adomat HH, Etinger SL, Twiddy AL, Neumann RD, Nelson CC, Guns ES and Wasan KM: Alterations in cholesterol regulation contribute to the production of intratumoral androgens during progression to castration-resistant prostate cancer in a mouse xenograft model. Prostate 70: 390-400, 2010.
11. Shahzad MM, Mangala LS, Han HD, Lu C, Bottsford-Miller J, Nishimura M, Mora EM, Lee JW, Stone RL, Pecot CV, *et al*: Targeted delivery of small interfering RNA using reconstituted high-density lipoprotein nanoparticles. Neoplasia 13: 309-319, 2011.
12. Zheng Y, Liu Y, Jin H, Pan S, Qian Y, Huang C, Zeng Y, Luo Q, Zeng M and Zhang Z: Scavenger receptor B1 is a potential biomarker of human nasopharyngeal carcinoma and its growth is inhibited by HDL-mimetic nanoparticles. Theranostics 3: 477-486, 2013.
13. Lobo MV, Huerta L, Ruiz-Velasco N, Teixeiro E, de la Cueva P, Celdrán A, Martín-Hidalgo A, Vega MA and Bragado R: Localization of the lipid receptors CD36 and CLA-1/SR-BI in the human gastrointestinal tract: Towards the identification of receptors mediating the intestinal absorption of dietary lipids. J Histochem Cytochem 49: 1253-1260, 2001.
14. Berlth F, Bollschweiler E, Drebber U, Hoelscher AH and Moenig S: Pathohistological classification systems in gastric cancer: Diagnostic relevance and prognostic value. World J Gastroenterol 20: 5679-5684, 2014.
15. Yu H and Xin Y: Down-regulated expressions of PPARγ and its coactivator PGC-1 are related to gastric carcinogenesis and Lauren's classification in gastric carcinoma. Chin J Cancer Res 25: 704-714, 2013.
16. Kwon OK, Kim SW, Chae HD, Ryu SW, Chung HY, Kim SW, Lee WK and Yu W: Validation of the 7th AJCC/UICC staging system for gastric cancer and a proposal for a new TNM system based on a prognostic score: A retrospective multicenter study. Ann Surg Treat Res 91: 295-302, 2016.
17. Bogan RL and Hennebold JD: The reverse cholesterol transport system as a potential mediator of luteolysis in the primate corpus luteum. Reproduction 139: 163-176, 2010.
18. Remmele W and Stegner HE: Recommendation for uniform definition of an immunoreactive score (IRS) for immunohistochemical estrogen receptor detection (ER-ICA) in breast cancer tissue. Pathologe 8: 138-140, 1987 (In German).
19. Hu B, El Hajj N, Sittler S, Lammert N, Barnes R and Meloni-Ehrig A: Gastric cancer: Classification, histology and application of molecular pathology. J Gastrointest Oncol 3: 251-261, 2012.
20. Ghandur-Mnaymneh L, Paz J, Roldan E and Cassady J: Dysplasia of nonmetaplastic gastric mucosa. A proposal for its classification and its possible relationship to diffuse-type gastric carcinoma. Am J Surg Pathol 12: 96-114, 1988.

21. Cristescu R, Lee J, Nebozhyn M, Kim KM, Ting JC, Wong SS, Liu J, Yue YG, Wang J, Yu K, *et al*: Molecular analysis of gastric cancer identifies subtypes associated with distinct clinical outcomes. Nat Med 21: 449-456, 2015.
22. Cancer Genome Atlas Research Network: Comprehensive molecular characterization of gastric adenocarcinoma. Nature 513: 202-209, 2014.
23. Shah MA, Khanin R, Tang L, Janjigian YY, Klimstra DS, Gerdes H and Kelsen DP: Molecular classification of gastric cancer: A new paradigm. Clin Cancer Res 17: 2693-2701, 2011.
24. Shen H, Newmann AS, Hu Z, Zhang Z, Xu Y, Wang L, Hu X, Guo J, Wang X and Wei Q: Methylenetetrahydrofolate reductase polymorphisms/haplotypes and risk of gastric cancer: A case-control analysis in China. Oncol Rep 13: 355-360, 2005.
25. Guo E, Chen L, Xie Q, Chen J, Tang Z and Wu Y: Serum HDL-C as a potential biomarker for nodal stages in gastric cancer. Ann Surg Oncol 14: 2528-2534, 2007.
26. Tamura T, Inagawa S, Hisakura K, Enomoto T and Ohkohchi N: Evaluation of serum high-density lipoprotein cholesterol levels as a prognostic factor in gastric cancer patients. J Gastroenterol Hepatol 27: 1635-1640, 2012.
27. Caruso MG, Notarnicola M, Cavallini A and Di Leo A: 3-Hydroxy-3-methylglutaryl coenzyme A reductase activity and low-density lipoprotein receptor expression in diffuse-type and intestinal-type human gastric cancer. J Gastroenterol 37: 504-508, 2002.
28. Barresi V, Giuffre G, Vitarelli E, Todaro P and Tuccari G: Caveolin-1 immuno-expression in human gastric cancer: Histopathogenetic hypotheses. Virchows Arch 453: 571-578, 2008.
29. Han J, Parsons M, Zhou X, Nicholson AC, Gotto AM Jr and Hajjar DP: Functional interplay between the macrophage scavenger receptor class B type I and pitavastatin (NK-104). Circulation 110: 3472-3479, 2004.
30. Zhao SP, Wu ZH, Hong SC, Ye HJ and Wu J: Effect of atorvastatin on SR-BI expression and HDL-induced cholesterol efflux in adipocytes of hypercholesterolemic rabbits. Clin Chim Acta 365: 119-124, 2006.
31. Tsuruoka H, Khovidhunkit W, Brown BE, Fluhr JW, Elias PM and Feingold KR: Scavenger receptor class B type I is expressed in cultured keratinocytes and epidermis. Regulation in response to changes in cholesterol homeostasis and barrier requirements. J Biol Chem 277: 2916-2922, 2002.
32. Kimura T, Mogi C, Tomura H, Kuwabara A, Im DS, Sato K, Kurose H, Murakami M and Okajima F: Induction of scavenger receptor class B type I is critical for simvastatin enhancement of high-density lipoprotein-induced anti-inflammatory actions in endothelial cells. J Immunol 181: 7332-7340, 2008.
33. Mardones P, Pilon A, Bouly M, Duran D, Nishimoto T, Arai H, Kozarsky KF, Altayo M, Miquel JF, Luc G, *et al*: Fibrates down-regulate hepatic scavenger receptor class B type I protein expression in mice. J Biol Chem 278: 7884-7890, 2003.
34. Lan D and Silver DL: Fenofibrate induces a novel degradation pathway for scavenger receptor B-I independent of PDZK1. J Biol Chem 280: 23390-23396, 2005.
35. Yuan B, Wu C, Wang X, Wang D, Liu H, Guo L, Li XA, Han J and Feng H: High scavenger receptor class B type I expression is related to tumor aggressiveness and poor prognosis in breast cancer. Tumour Biol 37: 3581-3588, 2016.
36. Twiddy AL, Cox ME and Wasan KM: Knockdown of scavenger receptor class B type I reduces prostate specific antigen secretion and viability of prostate cancer cells. Prostate 72: 955-965, 2012.
37. Schörghofer D, Kinslechner K, Preitschopf A, Schütz B, Röhrl C, Hengstschläger M, Stangl H and Mikula M: The HDL receptor SR-BI is associated with human prostate cancer progression and plays a possible role in establishing androgen independence. Reprod Biol Endocrinol 13: 88, 2015.
38. Kitadai Y, Sasaki A, Ito M, Tanaka S, Oue N, Yasui W, Aihara M, Imagawa K, Haruma K and Chayama K: *Helicobacter pylori* infection influences expression of genes related to angiogenesis and invasion in human gastric carcinoma cells. Biochem Biophys Res Commun 311: 809-814, 2003.