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Association of HMGB1 Gene Polymorphisms with Risk of Colorectal Cancer in a Chinese Population

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Statistical Analysis C
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Background: Colorectal cancer (CRC) is one of the leading causes of cancer-related deaths worldwide. More advanced work is required in the detection of biomarkers for CRC susceptibility and prognosis. High-mobility group box-1 (HMGB1) is an angiogenesis-related gene reported to be associated with the development of CRC. The direct evidence of HMGB1 gene polymorphisms as biomarkers for CRC has not been reported previously.

Material/Methods: A total of 240 CRC patients and 480 healthy controls were periodically enrolled. DNA was extracted from blood specimens. The distributions of SNPs of HMGB1 were determined by using the polymerase chain reaction restriction fragment length polymorphism (PCR-RFLP) assay.

Results: In this case-control study, we observed a significant association between overall CRC risk and SNP rs2249825 (CG *vs.* CC and GG *vs.* CC). Participants carrying both rs2249825 CG (OR, 2.67; 95% CI, 1.89 to 3.78) and rs2249825 GG genotypes (OR, 2.32; 95% CI, 1.13 to 4.73) had a significantly increased risk of developing CRC compared to those carrying GG genotype. rs2249825 was associated with the risk of CRC in the dominant model but not in the recessive model. However, we found no significant differences in the rs1412125 or rs1045411 polymorphisms in the HMGB1. Advanced analyses showed that the number of rs2249825 G alleles showed a significant relationship with risk of CRC.

Conclusions: Our results show an association between HMGB1 rs2249825 SNP and CRC incidence in the Chinese Han population. However, population-based studies with more subjects and prognostic effects are needed to verify the association of HMGB1 SNPs with CRC susceptibility, severity, and long-term prognosis.

MeSH Keywords: Case-Control Studies • Colorectal Neoplasms, Hereditary Nonpolyposis • Diagnosis • HMGA1a Protein

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Background

Cancer accounts for over 10% of all deaths and colorectal cancer (CRC) is one of the leading causes of cancer-related deaths worldwide [1]. CRC is one of the most frequent malignancies in the world, and despite significantly improved treatment modalities, CRC remains a major cause of cancer mortality [2]. The prognosis of CRC was currently quite poor due to the high incidence and lack of effective diagnosis and treatment methods [3,4]. Worldwide, a significant increase in the CRC incidence rate has been detected over the last decade, especially in developing countries. Prediction the prognosis of CRC patients is difficult [5]. The Tumor Node and Metastasis (TNM) staging system can provide certain clues regarding the prognosis of CRC [6]. Recent studies indicated that the discovery and application of sensitive and specific biomarkers could improve the outcome of CRC patients [7]. Although relevant studies have been conducted, very few useful biomarkers have been identified for early diagnosis or predication of outcome [3,8]. More research is needed in the detection of biomarkers for CRC susceptibility and prognosis.

Although many studies have been conducted on the etiology of CRC, it remains poorly understood. Several *in vivo* and *in vitro* studies have been conducted to detect potential biologically plausible pathways in the development of CRC, but the detailed physiopathological mechanisms of CRC are still quite unclear [9]. It has been reported that reduced apoptosis, abnormal proliferation, and angiogenesis are common pathways for some cancers, including CRC [10]. Thus, research on CRC angiogenesis would help to explain its development and metastasis, as well as predicting CRC patient prognosis. Recently, high mobility group box-1 (HMGB1), which is an angiogenesis-related gene, was reported to be associated with the development of CRC [11]. It has also been proved that HMGB1 is a potent cytokine that involved in CRC angiogenesis [12]. HMGB1 has long been recognized as a pro-angiogenesis factor leading to the generation of vascular endothelial growth factor (VEGF) in colon cancer. Since VEGF is known as one of the key regulators of CRC, this indirect association indicates that HMGB1 may induce angiogenesis in CRC [13,14]. HMGB1 is also related with cell proliferation [15]. The signaling pathways related with cell proliferation for HMGB1 in cancer development may be involved downstream. HMGB1 can increase cellular proliferation via the HMGB1/RAGE/NF-κB pathway [16].

Polymorphisms can potentially influence the expression of hundreds of genes and can influence various kinds of gene function [17–19]. A variety of SNPs in different genes were reported to be related to cancer development and are regarded as useful cancer biomarkers, and the use of SNP in cancer diagnosis has been widely reported [20,21]. For instance, in a recent meta-analysis, the data suggested that the SNPs in adiponectin gene (including ADIPOQ rs2241766 T>G, rs1501299 G>T, and rs266729 C>G SNPs) are correlated with an increased risk of CRC [19]. SNPs in HMGB1 regions have been reported to be associated with differential expression of HMGB1 and may be functionally important [22]. Recently increasing evidence suggests that genetic alterations in HMGB1 could modify biological pathways and may be associated with cancer development and progression [23]. Considering the feasibility and stability of SNPs detection, it may be a better strategy to use HMGB1 SNPs in the early diagnosis of CRC. However, there is currently no direct evidence of HMGB1 gene polymorphisms as biomarkers for CRC. The aim of this study was to evaluate the association between the different HMGB1 SNPs and the risk of CRC and to determine the clinicopathological characteristics of CRC patients with different genotypes.

Material and Methods

Ethics statement

This research was approved by the Institutional Review Board of Shandong University and the informed consent form was also approved by the Ethics Committee of Shandong University. All participation was voluntary and subjects provided written informed consent prior to taking part in this study.

Study subjects

This was a hospital-based case-control study. From 2010 to 2014, 240 patients diagnosed with CRC in the Department of Anoproctology, the Second Hospital of Shandong University were recruited. The cases were inpatients newly diagnosed with histologically confirmed CRC, without any familial history of cancer. Patients with secondary or recurrent malignancies were excluded from this study. Detailed clinical features, including the age at diagnosis, sex, body mass index, alcohol intake, tobacco smoking, and tumor characteristics were obtained from the medical records and interview of patients. A structured questionnaire on demographics and environmental exposure was used by trained interviewers through face-to-face interviews with the patients. A total of 480 age- (±5 years) and sex-matched controls were included from the cancer-free population in a 1:2 ratio. Control subjects with any previous history of cancer or severe digestive, endocrinic and cardiovascular diseases were excluded. All subjects were genetically unrelated ethnic Han Chinese.

In general, 5 ml of venous blood was collected from each participant for genomic DNA extraction performed as soon as possible after withdrawal. The venous blood samples were centrifuged at 965 g for 15 min. Genomic DNA from each sample was extracted using a commercial extraction kit (Bioteke Corporation,

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Beijing, China) according to the manufacturer's directions. The extracted DNA was stored in –70°C freezer at the Department of Anoproctology, the Second Hospital of Shandong University until use. The storage time was less than 3 days.

Genotyping

The distributions of SNPs of HMGB1 were determined by polymerase chain reaction restriction fragment length polymorphism (PCR-RFLP) assay. All PCR and sequencing primers were synthesized by DNA-Technology A/S (Aarhus, Denmark). The DNA sequence and polymorphism detection primers were:
rs1412125
Forward: ATGATTAGTAGAGGGAAGCAGA GG,
Reverse: -ACAGACTTCCCTTTTTTTTCACTC;
rs2249825 Forward: TGTCTGATTTTACGGAGGTTGAT;
Reverse: GTTTGCACAAAAAATGCATATGAT;
rs1045411
Forward: ATGGAAGTGGGAGGCAATTTAG;
Reverse: CATTTTAAAAGTTGGCCCAATT.

PCR condition

The PCR assays were performed on an ABI 9600 device (Applied Biosystems, USA) following the manufacturer's directions. The final relational volume was 5 ml and it contained 0.25 ml primer, 0.125 ml probe, 2 ml PCR mixture reagent, and 25 ng DNA. The cycling condition for HMGB1 SNP rs1045411G consisted of an initial denaturing step at 94°C for 5 min followed by 30 cycles of 94°C 1 min, 62°C 1 min, 72°C 1 min, and a final 5-min extension at 72°C. Cycling condition for (rs2249825 and rs1412125) consisted of an initial denaturing step at 94°C for 5 min followed by 30 cycles of 94°C 1 min, 62°C 1 min, 72°C 1 min, and a final 5-min extension at 72°C. The cycling condition for rs11614913 consisted of an initial denaturing step at 94°C for 5 min followed by 35 cycles of 94°C for 1 min, 63°C for 1 min, 72°C for 1 min, and a final 5-min extension at 72°C. Representative PCR products were subjected to direct DNA sequencing in an ABI Prism 310 Sequence (Applied Biosystems, USA) to confirm the accuracy of this method.

Statistical analysis

Goodness-of-fit χ^2 test was used to assess the Hardy-Weinberg equilibrium in this study. The significance of the differences of genotypes and allelic frequencies in the CRC cases and healthy controls was determined using 2×2 tables and a standard χ^2 test. Odds ratios (OR) and 95% confidence intervals (95% CI) were used in the calculation of the corresponding χ^2 distribution test. The χ^2 test was used to assess the association of clinicopathologic characteristics and HMGB1 genotypes and allelic frequencies among CRC patients and healthy cases. The paired *t* test was used for comparison of the mean of continuous variables. All statistical tests were two-sided, and a probability level of $P<0.05$ was considered to be statistically significant. Data analysis was done using SPSS 11.0 software (SPSS, Inc.).

Results

Participant information

A total of 720 participants (346 males and 374 females) were included in this study, with the mean age of 52.3±10.7 in CRC group and 53.6±11.4 in the control group. Compared with the control group, no significant differences were detected in body mass index, alcohol consumption, vegetable intake, or meat intake. However, smoking status was more common among the patients with CRC. When the TNM stage of the CRC cases were considered, 18 cases (7.50%) were in stage I, 21 cases (8.87%) were in stage II, 172 cases (71.67%) were in stage III, and a total of 29 cases (12.08%) were in stage IV. Clinicopathologic characteristics of the study participants are described in Table 1.

The genotype frequencies of the 3 HMGB1 polymorphisms between CRC patients and healthy controls

The genotypic and allelic distributions of all 3 HMGB1 SNPs in CRC cases and healthy controls are summarized in Table 2. The observed genotype frequencies for the SNP agreed with those expected from Hardy-Weinberg equilibrium in CRC cases ($P=0.26$) and controls ($P=0.51$. We first evaluated the association between the 3 HMGB1 SNPs and risk of CRC. In general, participants carrying both rs2249825 CG (OR, 2.67; 95% CI, 1.89 to 3.78) and rs2249825 GG genotypes (OR, 2.32; 95% CI, 1.13 to 4.73) had a significantly increased risk of developing CRC compared to GG genotype, after adjusting for age and sex. In the dominant model, we found that CG + GG cases have a significantly increased risk of CRC compared with the CC cases (OR, 2.61; 95% CI, 1.88 to 3.63). In the recessive model no significant difference was detected (OR, 1.71; 95% CI=0.85 to 3.46).

No significant differences were detected in the rs1412125 or rs1045411 polymorphisms in the HMGB1. For rs1412125, compared with the TT genotype, TC genotype and CC genotype demonstrated no significant association (OR=1.57, 95 CI=0.70 to 3.52, P=0.248 and OR=1.16, 95% CI=0.85 to 1.58, P=0.185, respectively). For rs1045411, compared with the GG genotype, GA genotype and AA genotype demonstrated no significant association (OR=0.79, 95 CI=0.57 to 1.09, P=0.088 and OR=1.45, 95% CI=0.70 to 3.30, P=208, respectively). Similarly, the genotype distributions of rs1412125 and rs1045411 were not significantly different between cases and controls in either

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Table 1. Clinicalpathologic features of colorectal carcinoma patients and healthy controls.

Variables	Cases (n=240)	Percentage (%)	Control (n=480)	Pecentage (%)	P value
Age (years, year ±SD)	52.3±10.7		53.6±11.4		0.142
<60	113	47.03	225	46.88	0.465
≥60	127	52.97	255	53.12	
Gender					
Male	126	76.71	220	52.27	0.091
Female	114	23.33	260	15.73	
BMI	20.7±3.8		21.0±4.2		0.351
Smoking status					
Never	81	33.75	231	48.13	**<0.0001**
Ever	159	66.25	249	51.87	
Alcohol consumption					
Never	124	51.67	252	0.525	0.883
Ever	116	48.33	228	0.475	
Vegetable intake					
<3 times/w	74	30.06	149	37.29	0.955
≥3 times/w	166	69.94	331	62.71	
Meat intake					
<3 times/w	82	32.80	179	30.80	0.260
≥3 times/w	168	53.33	301	36.00	
TNM stage					
I	18	7.50			
II	21	8.87			
III	172	71.67			
IV	29	12.08			
Tumor size					
<5 cm	111	46.25			
≥5 cm	129	53.75			
Lymph node metastasis					
Yes	201	83.75			
No	39	16.25			

w – week; BMI – body mass index.

the dominant or recessive models. Taken together, these data suggest that rs2249825, but not rs1412125 or rs1045411, polymorphism was associated with the risk of CRC (Table 2).

Allele distribution of HMGB1 SNPs in CRC cases and controls

The number and distribution of HMGB1 SNPs were also detected in this study. The number of rs2249825 G alleles showed a significant dose-response relationship with the risk of CRC (OR=2.14, 95% CI=1.63 to 2.82, P<0.001), but the C allele in

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Table 2. Genotypefrequency of HMGB1 polymorphism in patients with colorectal cancer and controls.

SNP	Genotype	Cases	Percentage (%)	Control	Pecentage (%)	P value	OR (95% CI)
rs2249825 C/G	CC	131	54.58	364	75.83	–	Reference
	CG	94	39.17	98	20.42	**<0.001**	**2.67 (1.89 to 3.78)**
	GG	15	6.25	18	3.75	**<0.001**	**2.32 (1.13 to 4.73)**
	Dominant	–	–	–	–	**<0.001**	**2.61 (1.88 to 3.63)**
	Recessive	–	–	–	–	0.095	1.71 (0.85 to 3.46)
rs1412125 T/C	TT	126	52.50	270	56.25	–	Reference
	TC	103	24.72	195	40.63	0.248	1.13 (0.82 to 1.56)
	CC	11	4.58	15	3.12	0.185	1.57(0.70 to 3.52)
	Dominant	–	–	–	–	0.191	1.16 (0.85 to 1.58)
	Recessive	–	–	–	–	0.216	1.49 (0.67 to 3.29)
rs1045411 G/A	GG	144	60.00	268	55.83	–	Reference
	GA	82	34.17	194	40.42	0.088	0.79 (0.57 to 1.09)
	AA	14	5.83	18	3.75	0.208	1.45 (0.70 to 3.30)
	Dominant	–	–	–	–	0.162	0.84 (0.62 to 1.15)
	Recessive	–	–	–	–	0.139	1.59 (0.78 to 3.25)

Table 3. Allele distribution of HMGB1 single nucleotide polymorphisms in colorectal carcinoma patients and healthy controls.

SNP	Allele	Cases	Percentage (%)	Controls	Pecentage (%)	P value	OR (95% CI)
rs2249825 C/G	C	356	74.17	826	80.04	Reference	Reference
	G	124	25.83	134	19.96	**<0.001**	**2.14 (1.63 to 2.82)**
rs1412125 T/C	T	355	73.96	735	76.56	Reference	Reference
	C	125	26.04	225	23.44	0.154	1.15 (0.89 to 1.48)
rs1045411 G/A	G	370	77.08	730	76.04	Reference	Reference
	A	110	2.92	239	23.96	0.356	0.94 (0.73 to 1.22)

rs1412125 and A allele in rs1045411 showed no significant association with the risk of CRC (Table 3).

Discussion

CRC is one of the most common gastrointestinal carcinomas worldwide. Over the past decades, CRC was the leading cause of cancer-related deaths. Although the effect of HMGB1 on the development of CRC has been widely studied, the distribution HMGB1 SNPs in CRC cases and controls has not received much attention. In this case-control study, we observed a significant association between overall CRC risk and SNP rs2249825 (CG *vs.* CC and GG *vs.* CC). Participants carrying both rs2249825 CG (OR, 2.67; 95% CI, 1.89 to 3.78) and rs2249825 GG genotypes (OR, 2.32; 95% CI, 1.13 to 4.73) had a significantly increased risk of developing CRC compared to those with GG genotype. rs2249825 was associated with the risk of CRC in the dominant model but not in the recessive model. However, we found that no significant differences were detected in the rs1412125 or rs1045411 polymorphisms in HMGB1. To further explore the potential association of allele distribution of HMGB1 SNPs and risk of CRC, we performed an advanced analysis and found that the rs2249825 G allele showed a significant dose-response relationship with the risk of CRC (OR=2.14, 95% CI=1.63 to 2.82, P<0.001). These results indicate that among all the HMGB1 SNPs, rs2249825, but not other SNP sites, was associated with CRC risk.

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HMGB1 plays a critical role in various diseases and disorders, especially in inflammatory, immune responses, and hypoxia in the cancer microenvironment. However, there are conflicting reports about the roles of HMGB1 acting as both a tumor suppressor and an oncogenic factor in cancer. More knowledge is required about the role of HMGB1 in CRC tumorigenesis. In a recent study, genomic alterations of these genes were investigated through using the Cancer Genome Atlas (TCGA) database, utilizing 195 published CRC specimens. By utilizing a Cancer Array, containing 440 oncogenes and tumor suppressors to profile mRNA expression, RPN2 and HMGB1 displayed a higher genomic alteration frequency in CRC compared to 8 other major solid cancers [24]. In another study based immunohistochemical method with 86 colorectal cancer patients and 32 normal controls, it was found that HMGB1 expression in colorectal cancer is high, and its positive rate increases with lower differentiation, invasion, and metastasis [25]. Another study was conducted to investigate the *in vitro* effects of ulinastatin (UTI) on the proliferation, invasion, apoptosis, expression, and distribution of high mobility group box 1 (HMGB1) and the expression of nuclear factor κB (NF-κB) in human colon carcinoma LoVo cells. It was found that UTI inhibited the expression of HMGB1 and NF-κB, and decreased the cytoplasmic distribution of HMGB1 [26]. The prognostic effect of HMGB1 was also detected. It was reported that high HMGB1expression was associated with larger tumor volumes, higher rates of lymphatic invasion, more frequent lymph node metastases, and poorer prognoses for overall survival. Multivariate analyses showed that HMGB1expression was an independent prognostic indicator of overall survival [27].

The effects of HMGB1 on CRC development has also been studied [28]. Because the endothelium plays a pivotal role in the progression of solid tumors, it is important to study the effect HMGB1, which is an angiogenesis factor, on the tumor angiogenesis of CRC cells. In general, HMGB1 stimulates the expression of vascular endothelial growth factor and platelet-derived growth factor signaling, both *in vitro* and *in vivo*. Importantly, it was also shown that HMGB1 triggers and helps to sustain this proangiogenic gene expression program in ECs, additionally characterized by increased activity of matrix metalloproteinases, integrins, and nuclear factor-κB [29]. Another study was conducted to identify the specific enzyme and important sites for HMGB1 phosphorylation. Through screening the protein kinase C (PKC) family in a colon cancer cell line, a 3XFLAG-HMGB1 construct was used in pull-down experiments. Strong interactions between atypical PKCs and cytoplasm were detected. By using PKC inhibitors and siRNA experiments, it was found that the most critical PKC isotype that regulates HMGB1 secretion is PKC-ζ [30]. Autophagy plays a key role in the effect of anti-cancer drugs, and it was found that HMGB1-mediated autophagy modulates sensitivity of colorectal cancer cells to oxaliplatin via the MEK/ERK signaling pathway [31].

Previous studies have demonstrated that polymorphisms of certain genes can influence gene expression and biological functions. A total of 3 frequently used SNPs within the human HMGB1 gene have been obtained in this current study. A previous study examined the SNPs in HMGB1 gene in patients with oral squamous cell carcinoma (OSCC) and oral lichen planus (OLP). The data from 93 patients with OSCC, 53 patients with OLP, and 100 controls showed that HMGB1 polymorphism 1177G/C is be associated with tumor progression and recurrence-free survival in patients with OSCC [22]. Another study was conducted to detect HMGB1 production in response to *ex vivo* lipopolysaccharide (LPS) stimulation. It was reported that rs2249825 SNP and the haplotype TCG were significantly associated with LPS-induced HMGB1 production by peripheral blood leukocytes [32]. Thus, it was important for the evolution of HMGB1 SNPs as diagnostic biomarker of CRC and it is of interest for the detection of the value of HMGB1 SNPs for predicting the prognosis of CRC patients. However, how the SNPs in the HMGB1 gene influenced the progression of disorders is unclear. A study based on clinical samples reported that patients with rs2249825 GG genotype had significantly elevated levels of HMGB1 in chorionic villi compared to those with CG or CC genotype [33]. In the present study, we found that only SNP rs2249825 was associated with CRC incidence. Given that rs2249825 is associated with the expression of HMGB1, which would promote the development of CRC, it was natural to think that rs2249825 influences CRC development through modifying the expression of HMGB1. However, additional studies are required to prove this hypothesis.

Conclusions

Our results show an association between HMGB1 rs2249825 SNP and CRC incidence in the Chinese Han population. However, no significant association of the 2 other (rs1412125 and rs1045411 polymorphisms) SNPs and risk of CRC was detected. Advanced analyses showed that the number of rs2249825 G alleles showed a significant relationship with the risk of CRC. However, population-based studies with large numbers of subjects and prognostic effects are needed to verify the association of HMGB1 SNPs and CRC susceptibility, severity, and long-term prognosis.

Conflict of interest

We have no financial interest or conflict of interest in association with this work.

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