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ORIGINAL ARTICLE

Single nucleotide polymorphism rs2555639 in 15-PGDH and colorectal cancer metastasis

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Summary

Purpose: *To investigate the correlation between metastasis of colon cancer and the single nucleotide polymorphism (SNP) rs2555639 in nicotinamide adenine dinucleotide (NAD)+-dependent 15-hydroxyprostaglandin dehydrogenase (15-PGDH) (rs2555639).*

Methods: *We investigated the genotyping of peripheral blood genomic DNA in patients using the TaqMan probe method. The relationship between the genotype of 15-PGDH (rs2555639) and metastasis of colon cancer was analyzed.*

Results: *We noticed that rs2555639 TT polymorphism was significantly correlated with the susceptibility to colon cancer metastasis. Also, in the stratified analysis, we found similar results.*

Conclusion: *Our data suggested that the rs2555639 T allele is associated with increased risk of metastasis of colon cancer, which can be used as an indicator for colon cancer metastasis.*

Key words: *15-PGDH, rs2555639, colon cancer, metastasis*

Introduction

Metastatic colon cancer is one of the most common malignant tumors in China [1-3]. NAD+-dependent 15-hydroxyprostaglandin dehydrogenase (15-PGDH), an enzyme involved in prostaglandin (including PGE2) bio-inactivation, is lowly-expressed in several epithelial malignancies including metastatic colon cancer [4-6]. The enzyme is important in regulating the biological activity of prostaglandin [7]. Although its role in the suppression of colon tumorigenesis has been reported, little is known about the role of 15-PGDH in the process of tumor metastasis [8].

Recent studies have suggested that the T allele in the SNP of 15-PGDH (rs2555639) is a risk factor for the occurrence of colon cancer and patients with such genotype have shown low expression of 15-PGDH [9]. In this study we investigated the relationship between 15-PDGH rs2555639 gene polymorphism and metastatic colon cancer and analyzed the relationship between genotype and metastatic colon cancer for providing guidance for clinical treatment.

Methods

Ethical statements and patients

The patients with colon cancer treated at the Department of Gastroenterology, Shanxi Provincial Cancer Hospital from June 2014 to April 2016 were retrospectively analyzed. All patients were diagnosed according to clinical and pathological data. Ninety-five patients with colon cancer (51 men and 44 women), aged from 43 to 76

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years (mean 52) were studied. This study was approved by the Ethical Committee of Shanxi Provincial Cancer Hospital, and performed according to the principles of the Declaration of Helsinki. All the patients gave written informed consent to participate in the study.

DNA extraction and genotyping

Total DNA from patient peripheral blood was extracted with DNA Extraction Kits (Tiangen, Beijing, China) according to the instructions of the manufacturer. The rs2555639 polymorphism was performed by Taqman probe method according to previous report using Applied Biosystems ViiA™ 7 Real-Time PCR System [10]. The probe sequence was as follows: GATCCCGGAACCGGAATTGTCTCCCC/TTGGCGTTCCGGAAGTAGAAGCAGAG.

Statistics

All statistical analyses were performed using SPSS version 21.0 (IBM). The non-metastatic group was used as control group and the Hardy-Weinberg equilibrium (HWE) was measured by chi square (x^2) test. Comparisons between metastatic cases and control group were analyzed by chi-square test. Odds ratios (OR) and 95% confidence intervals (95% CI) for colon cancer metastasis and the association with SNP rs2555639 were assessed by binary logistic regression analysis and adjusted by age, gender and primary site. P value less than 0.05 was considered statistically significant.

Results

The study was consisted of 60 non-metastatic colon cancer patients and 35 patients with metastasis. The non-metastasis control group was quantified by Hardy-Weinberg equilibrium (x^2=0.931, p=0.335). The demographic data of each group as well as the clinical data are shown in Table 1.

The allele frequencies for rs2555639 were determined in metastatic colon cancer patients and controls. The frequencies of rs2555639 C allele in the controls was 55.0% compared with 32.9% in metastatic patients (p=0.004). Moreover, we found a significant association between rs2555639 TT polymorphism and the susceptibility to colon cancer metastasis (OR=7.798, 95% CI=1.837-33.096, p=0.005). Also, we assessed the data using the dominant model (OR=2.680, 95% CI=1.066-6.740, p=0.036) and the recessive model (OR=5.480, 95% CI=1.468-20.458, p=0.011), which was coincident as shown in Table 2.

In addition, the association between rs2555639 and the susceptibility to colon cancer metastasis were further evaluated by stratified analysis of clinical features including age, gender, primary cancer site, T stages, N stages and received chemotherapy or not. As shown in Table 3, there was no obvious

Table 1. Distribution of selected characteristics of patients with or without colorectal cancer metastasis

Characteristics	*Non-metastatic patients n (%)*	*Metastatic patients n (%)*	*p value*
No. patients	60	35	
Age (years)			0.719
≤60	32 (53.3)	20 (57.1)	
>60	28 (46.7)	15 (42.9)	
Gender			0.234
Male	35 (58.3)	16 (45.7)	
Female	25 (41.7)	19 (54.3)	
Primary site			0.654
Colon	32 (53.3)	17 (48.6)	
Rectum	28 (46.7)	18 (51.4)	
pT status			<0.001
pT2-3	31 (51.7)	6 (17.1)	
pT4	29 (48.3)	29 (82.9)	
pN status			<0.001
N0	41 (68.3)	7 (20.0)	
N1-N2	19 (31.7)	28 (80.0)	
Adjuvant chemotherapy			0.223
None	20 (33.3)	6 (17.1)	
FOLFOX	32 (53.3)	24 (68.6)	
XELOX	8 (13.4)	5 (14.3)	

FOLFOX: 5-Fluorouracil/Leucovorin/Oxaliplatin; XELOX: Capecitabine/Oxaliplatin

different association between the rs2555639 variant and colon cancer metastasis among gender, primary site, T and N clinical stages, however, we noticed that in younger patients (≤60 years), TT allele was significantly associated with colon cancer metastasis (OR=4.605, 95% CI=1.214-17.468, p=0.025). Similar results were found in patients who had already received chemotherapy (OR=3.372, 95% CI=1.116-10.185, p=0.031).

Discussion

Metastasis is the major cause of cancer-related death and numerous studies have focused on screening and targeting new markers of metastasis [11-13]. However, the precise mechanism underlying metastasis remains elusive [14]. The inflammation factor COX2 and the correlation between colon cancer metastasis have been already demonstrated

Table 2. Logistic regression analysis of associations between the frequency of rs2555639 and colorectal cancer metastasis status

Genotype	*Metastasis n (%)*	*Non-metastasis n (%)*	*OR (95% CI)*[1]	*p value*
PSCA rs2294008				
CC	3 (8.6)	20 (33.3)	1	
CT	17 (48.6)	26 (43.3)	4.349 (1.097-17.236)	0.036
TT	15 (42.8)	14 (23.4)	7.798 (1.837-33.096)	0.005
Dominant model (CC/CT vs. TT)			2.680 (1.066-6.740)	0.036
Recessive model (CC vs. CT/TT)			5.480 (1.468-20.458)	0.011
Allele frequency			2.498 (1.350-4.619)	0.004
T allele	47 (67.1)	54 (45.0)		
C allele	23 (32.9)	66 (55.0)		

OR: odds ratio, CI: confidence interval. [1]ORs and p values were obtained after the adjustment of age, gender and primary site.

Table 3. Stratified analysis of the association between rs2555639 and colorectal cancer metastasis

Variables	*Rs2555639 (Metastasis/Non-metastasis)*		*OR (95% CI)*[1]	*p value*
	CC/CT	*TT*		
Age, years				
≤60	11/27	9/5	4.605 (1.214-17.468)	0.025
>60	9/19	6/9	1.471 (0.390-5.542)	0.569
Gender				
Male	8/26	8/9	3.364 (0.882-12.835)	0.076
Female	12/20	7/5	2.598 (0.630-10.718)	0.187
Primary site				
Colon	10/24	7/8	3.319 (0.740-13.322)	0.121
Rectum	10/22	8/6	2.978 (0.802-11.058)	0.103
T stages				
T2-3	4/23	2/8	4.851 (0.318-73.921)	0.256
T4	16/23	13/6	3.234 (0.970-10.785)	0.056
N stages				
N0	4/32	3/9	3.656 (0.588-22.743)	0.164
N1-2	16/14	12/5	2.163 (0.590-7.936)	0.245
Chemotherapy[2]				
None	4/14	2/6	1.255 (0.123-12.839)	0.848
FOLFOX/ XELOX	16/32	13/8	3.372 (1.116-10.185)	0.031

[1]ORs and p values were obtained after adjustment of age, gender and tumor primary site. [2]We combined the patients that received FOLFOX or XELOX and made the analysis.

in various studies [15,16]. 15-PDGH is identified as a metabolic suppressor of COX-2 and potential tumor suppressor gene [17,18]. Recently, several genetic variants in 15-PDGH were found and the associations between these SNPs and diseases were needed to be further elucidated [9,19,20].

In the present study we showed the evidence of the association between the rs2555639 T allele polymorphism and the susceptibility of colorectal cancer metastasis. Previous reports have demonstrated that this allele might be involved in decreasing 15-PGDH expression, since it is mapped on the 17 kb upstream of the 5'UTR of 15-PDGH gene, which was presumed the regulatory region [9]. These results highlighted the functional roles of genetic variants in modulating gene expression. We noticed that rs2555639 T allele had the potential to be a potential functional and metastasis variant. Moreover, in the younger patient subgroup (≤60 years), rs2555639 was significantly associated with CRC metastasis rather than in the older patient subgroup. This finding might be useful as a biomarker since the incident of CRC metastasis in younger patients has increased recently.

As the chemotherapy of CRC is well established, we assessed the association between rs2555639 and risk of CRC metastasis in patients who received chemotherapy or not. Interestingly, rs2555639 was significantly associated with metastasis in chemotherapy patients. This could be attributed to the administration of chemotherapy after metastasis and surgery failure. Therefore, the metastatic rate was significantly higher in the stratified chemotherapy group and this may affect the statistics. Another reason might be the biological roles of rs2555639 in regulating inflammatory factors which lead to diverse chemotherapy effects [21].

Limitations of the present study should be acknowledged. First, we only evaluated the association between 15-PDGH rs2555639 and the risk of CRC metastasis in a relatively small population. Thus, we should enlarge the number of cases and evaluate whether the association of rs2555639 with colorectal cancer metastasis was comparable. Second, although previous studies reported that rs2555639 was associated with colon cancer risk in European population, we still need to assess the association in Chinese population and in a further study we would add the normal group as control. In addition, we noticed that the frequency of total C allele in our study was higher compared to previous reports (46.8 vs. 34.5%), mainly due to the patients we selected. These might lower our ability to detect sufficient statistical significance.

In summary, our results suggested that the rs2555639 of 15-PDGH was associated with colorectal cancer metastasis and should lead to further studies to validate the association of rs2555639 with predisposition to colorectal cancer metastasis in other groups, as well as to investigate the biological functions of rs2555639 in colorectal cancer development and metastasis.

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Conflict of interests

The authors declare no conflict of interests.

References

1. Chen W, Zheng R, Baade PD et al. Cancer statistics in China, 2015. CA Cancer J Clin 2016;66:115-32.
2. Moghadamyeghaneh Z, Hanna MH, Hwang G et al. Outcomes of colon resection in patients with metastatic colon cancer. Am J Surg 2016;212:264-71.
3. Auyeung KK, Ko JK. Angiogenesis and oxidative stress in metastatic tumor progression: pathogenesis and novel therapeutic approach of colon cancer. Curr Pharm Des 2017;23:3952-61.
4. Yao L, Chen W, Song K et al. 15-hydroxyprostaglandin dehydrogenase (15-PGDH) prevents lipopolysaccharide (LPS)-induced acute liver injury. PLoS One 2017;12:e0176106.
5. Yang DH, Ryu YM, Lee SM et al. 15-Hydroxyprostaglandin dehydrogenase as a marker in colon carcinogenesis: analysis of the prostaglandin pathway in human colonic tissue. Intest Res 2017;15:75-82.
6. Hu M, Li K, Maskey N et al. 15-PGDH expression as a predictive factor response to neoadjuvant chemotherapy in advanced gastric cancer. Int J Clin Exp Pathol 2015;8:6910-8.
7. Mehdawi LM, Prasad CP, Ehrnstrom R, Andersson T, Sjolander A. Non-canonical WNT5A signaling up-regulates the expression of the tumor suppressor 15-PGDH and induces differentiation of colon cancer cells. Mol Oncol 2016;10:1415-29.
8. Pereira C, Queiros S, Galaghar A et al. Influence of Genetic Polymorphisms in Prostaglandin E2 Pathway

(COX-2/HPGD/SLCO2A1/ABCC4) on the Risk for Colorectal Adenoma Development and Recurrence after Polypectomy. Clin Transl Gastroenterol 2016;7:e191.

9. Thompson CL, Fink SP, Lutterbaugh JD et al. Genetic variation in 15-hydroxyprostaglandin dehydrogenase and colon cancer susceptibility. PLoS One 2013;8:e64122.
10. Gaedigk A, Freeman N, Hartshorne T et al. SNP genotyping using TaqMan technology: the CYP2D6*17 assay conundrum. Sci Rep 2015;5:9257.
11. Seguin L, Desgrosellier JS, Weis SM, Cheresh DA. Integrins and cancer: regulators of cancer stemness, metastasis, and drug resistance. Trends Cell Biol 2015;25:234-40.
12. Matthaiou S, Kostakis ID, Kykalos S et al. KISS1 and KISS1R expression in primary and metastatic colorectal cancer. J BUON 2018;23:598-603.
13. Liu CC, Cai DL, Sun F et al. FERMT1 mediates epithelial-mesenchymal transition to promote colon cancer metastasis via modulation of beta-catenin transcriptional activity. Oncogene 2017;36:1779-92.
14. Velipasalar O, Kocoglu H, Hursitoglu M, Tural D. A young woman with metastatic colon cancer presenting with elevated serum beta human chorionic gonadotropin. JBUON 2017;22:285.
15. Liu S, Zhang C, Zhang K et al. FOXP3 inhibits cancer stem cell self-renewal via transcriptional repression of COX2 in colorectal cancer cells. Oncotarget 2017;8:44694-704.
16. Ng K, Meyerhardt JA, Chan AT et al. Aspirin and COX-2 inhibitor use in patients with stage III colon cancer. J Natl Cancer Inst 2015;107:345.
17. Yan M, Rerko RM, Platzer P et al. 15-Hydroxyprostaglandin dehydrogenase, a COX-2 oncogene antagonist, is a TGF-beta-induced suppressor of human gastrointestinal cancers. Proc Natl Acad Sci U S A 2004;101:17468-73.
18. Ding Y, Tong M, Liu S, Moscow JA, Tai HH. NAD+-linked 15-hydroxyprostaglandin dehydrogenase (15-PGDH) behaves as a tumor suppressor in lung cancer. Carcinogenesis 2005;26:65-72.
19. Uppal S, Diggle CP, Carr IM et al. Mutations in 15-hydroxyprostaglandin dehydrogenase cause primary hypertrophic osteoarthropathy. Nat Genet 2008;40:789-93.
20. Frank B, Hoeft B, Hoffmeister M et al. Association of hydroxyprostaglandin dehydrogenase 15-(NAD) (HPGD) variants and colorectal cancer risk. Carcinogenesis 2011;32:190-6.
21. Pereira C, Queiros S, Galaghar A et al. Genetic variability in key genes in prostaglandin E2 pathway (COX-2, HPGD, ABCC4 and SLCO2A1) and their involvement in colorectal cancer development. PLoS One 2014;9:e92000.