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Association between Type 2 Diabetes and KRAS Mutation Status of Colorectal Cancer

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Abbreviations: CRC: Colorectal Cancers; T2DM: Type 2 Diabetes; MPE: Molecular Pathological Epidemiology; MetS: Metabolic Syndrome; SRCC: Signet-Ring Cell Carcinoma; FPG: Fasting Plasma Glucose; TG: Triglycerides; HDL: High-Density Lipoprotein Cholesterol; FGICH: Family Gastrointestinal Cancer History; ADA: American Diabetes Association; BMI: Body Mass Index; AC: Adenocarcinoma; SD: Standard Deviation; ORs: Odds Ratio; CIs: Confidence Intervals; SHBG: Sex Hormone Binding Globulin

ABSTRACT

Background: RAS genes (KRAS, NRAS) encoded proteins participate RAS-RAF-MAPK signaling pathway. Colorectal cancers (CRC) with RAS mutation are resistant to anti-EGFR monoclonal antibody therapy. The aim of the present study is to determine whether type 2 diabetes (T2DM) linked to RAS mutation of CRC.

Patients and Methods: KRAS, NRAS status was assessed in primary CRC (n=232) by ARMS-PCR (Amplication refractory mutation system).

Results: The mutation rate of KRAS in T2DM group was considerably higher than non-T2DM in overall patients (56.8% vs. 33.3%, P=0.007) and male patients (31.0% vs. 61.9%, P=0.007). Univariately, T2DM was significantly associated with KRAS mutation in overall patients (OR=2.63, 95% CI: 1.28-5.37, P=0.008) and male patients (OR=3.61, 95% CI: 1.38-9.47, P=0.009), but not in female patients. T2DM did not significantly associated with NRAS mutation status of CRC. Multivariate analysis retained the above significance. The most frequent KRAS mutations in T2DM group were codon 12, 34G>T, followed by codon 12, 35G>A. Moreover, for male patients, the NRAS mutation rate in patients with cigarette smoking habit was significantly higher than those without cigarette smoking habit (0% vs. 6.6%, P=0.042). In addition, mutation of RAS was significantly associated with pathological subtypes of CRC manifested by increased frequency of mucinous carcinoma and/or adenocarcinoma with mucinous components.

Conclusion: T2DM might influence carcinogenesis, progression and prognosis of CRC via promoting KRAS mutation and mucinous carcinoma phenotype.

Keywords: Type 2 Diabetes; Cigarette Smoking; KRAS; NRAS; Colorectal Cancer

Introduction

Previous study has suggested a link between type 2 diabetes mellitus (T2DM) and colorectal cancer (CRC) [1,2] but the molecular link between T2DM and CRC has not fully understood. Molecular pathological epidemiology (MPE) is a new research direction that focuses on special molecular markers of tumor initiation or progression in association with exposures of interest [3,4]. Kirsten rat sarcoma viral oncogene homolog (KRAS) and NRAS are kinase in RAS-RAF-MAPK signaling pathway. CRC with KRAS or NRAS mutation showed poor response to anti-EGFR monoclonal antibody therapy [5]. KRAS mutation occurs in about 40% of CRC and showed a high mutation rate in some subtypes of CRC including adenoma-like adenocarcinoma and mucinous carcinoma [6,7]. About 90% of KRAS mutation of CRC occurs in exon2 codon 12/13 [8]. Unlike KRAS, NRAS showed a low mutation

frequency in CRC [9]. T2DM is a component of metabolic syndrome (MetS), which including a set of metabolic disorders such as central obesity, hypertension, T2DM/hyperglycemia, and dyslipidemia [10]. Previous study indicated diabetes were linked to signet-ring cell carcinoma (SRCC) and colorectal adenocarcinoma (MAC) with components (mucinous, signet-ring cell, or neuroendocrine) [11]. KRAS mutation was detected at a higher frequency in mucinous carcinoma in comparison with classic colorectal adenocarcinoma (or non-mucinous adenocarcinoma) [9]. However, the association between T2DM and mutation of KRAS (or NRAS) has not been well-established so far. In the present study, we aimed to study the association between T2DM and KRAS or NRAS mutation in CRC.

Patients and Methods

Patients

The retrospective study included 232 cases (not including 11 cases excluded according exclusion criteria) of primary CRC from January 2013 to June 2021 in Zhejiang Provincial People's Hospital. Cases without clinical data such as diabetes status were excluded from the study (n=11). The patients were divided into subgroups of KRAS-mutation (mKRAS) and KRAS-wild-type (wKRAS), as well as NRAS-mutation (mNRAS) and NRAS-wild-type (wNRAS). The basic clinical data of the patients including gender, age, weight, height, blood pressure, fasting plasma glucose (FPG)/diabetic status, fasting plasma triglycerides (TG), and fasting plasma high-density lipoprotein cholesterol (HDL) were collected from the electronic medical records. Factors such as cigarette smoking habit, history of family gastrointestinal cancer (FGICH) were also collected. Pathological parameters including histological subtypes and histological grade of CRC were acquired from the pathological reports.

Ethics

The Ethics Committee of Zhejiang Provincial People's Hospital reviewed and approved the study (2021KT001, KY2019012). Anonymous clinical data were used in the analysis.

Mutation Assay

Genome DNA was extracted from paraffin-embedded tissue. Mutation of KRAS (n=232) and NRAS (n=225) was assayed by ARMS-PCR (Amplication refractory mutation system) using Human Gene Mutation Detection Kit for KRAS and NRAS (Products of Beijing ACCB Biotech, Beijing, China) according manufacturer's protocols. The KRAS Mutation Kit detects 7 hot mutations (Codon 12, 34G>T, 34G>A, 34G>C, 35G>T, 35G>A, 35G>C and Codon 13, 38G>A) of KRAS gene, which account for > 90% of known KRAS mutation. The NRAS Mutation Kit detects 9 kinds of mutations in coden 12, 13 and 61 of NRAS gene.

Diagnostic Criteria for T2DM

T2DM was diagnosed according the following criteria:

a) Patients had documented T2DM history before diagnosis of CRC;

b) Patients did not have a T2DM history but met the T2DM criteria of American Diabetes Association (ADA) [12]: FPG ≥ 7.0 mmol/L or Hemoglobin A1C ≥ 6.5%. Medical conditions such as dextrose and corticosteroids treatment that may elevate blood glucose levels were excluded.

Definition of Metabolic Syndrome

MetS were determined by presence of at least 3 of the following components according the criteria of China Diabetes Society (CDS) [10]:

a) Central obesity [body mass index (BMI) ≥ 25.0 kg/m^2

b) Dyslipidemia: hypertriglyceridemia (fasting plasma TG ≥ 1.7 mmol/L) and/or low HDL (fasting plasma HDL <0.9 mmol/L for men or <1.0 mmol/L for women).

c) Hypertension (systolic blood pressure ≥ 140 mm Hg and/or diastolic blood pressure ≥ 90 mm Hg and/or previously diagnosed as hypertension and under antihypertensive drug administration)

d) Hyperglycemia (FPG ≥ 6.10 mmol/L) or T2DM.

Pathological Subtypes

Colorectal adenocarcinomas were divided into 4 subtypes [13]:

(a) Classic adenocarcinoma

(b) Mucinous adenocarcinoma (MAC: ≥ 50% of the tumor area was composed of extracellular mucin)

(c) Signet-ring cell carcinoma (SRCC: ≥ 50% of the tumor area was composed of intracellular mucin)

(d) Adenocarcinoma (AC) with components (AC with presence but < 50% components of MAC and/or SRCC).

Histological Grade

In the present study, non-mucinous CRC (including classic adenocarcinoma and adenocarcinoma with mucinous/signet-ring cell components) were simply divided into low grade (≥ 50% glandular formation and including well to moderately-differentiated adenocarcinoma) and high grade (<50% gland formation or poorly-differentiated adenocarcinoma) [14]. Because mucinous carcinoma including SRCC and MAC were more aggressive than classic adenocarcinoma and not further graded [15].

Statistical Analysis

Continuous variable was expressed as mean ± standard deviation (SD) and analyzed by t-test. Categorized data were calculated as frequencies or percentage and analyzed by Chi-square test. If the theoretical frequency was less than five (T< 5) in any grid of a four-grid (or R´C) table, Fishers exact test was used for Chi-square test. Univariate or multivariate binary logistic regression models were used to estimate odds ratios (ORs) and 95% confidence intervals (CIs) for risks of KRAS mutation in association with T2DM and other factors (non-T2DM as reference). Two-sided value of P<0.05 was considered statistically significant. Statistical analysis was performed with SPSS software version 19.0 (IBM Corp., Armonk, NY).

Results

Baseline Characteristics

The mean age of the CRC patients was 59.9 (25-86 years). The overall T2DM rate of the CRC patients was 15.9% (37/232). Among the 37 T2DM patients, there were 25 patients with T2DM history before diagnosis of CRC, while 12 patients without T2DM history but met the criteria of ADA (FPG ≥ 7.0 mmol/L, n=10). The mutation rate of KRAS in T2DM group was considerably higher than non-T2DM in overall CRC patients (56.8% vs. 33.3%, P=0.007) (Table 1) and male patients (31.0% vs. 61.9%, P=0.007) (Table 2), but not in female patients. The KRAS mutation rate with cigarette smoking habit in male patients was slightly lower than those without cigarette smoking habit (29.0% vs. 41.3%, P=0.121) (Table 2). However, the NRAS mutation rate in male patients with cigarette smoking habit was significantly higher than those without cigarette smoking habit (0% vs. 6.6%, P=0.042) (Table 2). The results indicated cigarette smoking was positively associated with NRAS mutation in CRC. Factors including metabolic syndrome or its other individual components such as high BMI value (BMI ≥ 25 kg/m^2), hypertension, high TG, low HDL, as well as FGICH were not significantly associated with KRAS/NRAS mutation status (P> 0.05).

Table 1: Basic characteristic according to KRAS/NRAS status of colorectal cancer.

Factors	Overall	KRAS		P	Overall	NRAS		P
		WT	MU			WT	MU	
Age		59.4	60.8	0.441		59.9	63	0.512
Gender								
Female	95	58	37	0.622	92	88	4	0.594
Male	137	88	49		133	129	4	
MetS								
No	190	122	68	0.391	184	177	7	1
Yes	42	24	18		41	40	1	
BMI								
<25	167	104	63	0.978	161	155	6	1
≥25	58	36	22		57	55	2	
T2DM								
No	195	130	65	0.007	189	182	7	1
Yes	37	16	21		36	35	1	
TG								
< 1.7	172	109	63	0.814	166	161	5	0.435
≥ 1.7	60	37	23		59	56	3	
Low HDL								
No	136	83	53	0.475	132	127	5	1
Yes	96	63	33		93	90	3	
HBP								
No	124	78	46	0.993	121	117	4	1
Yes	108	68	40		104	100	4	
Cigarette								
No	170	102	68	0.126	164	160	4	0.138
Yes	62	44	18		61	57	4	

FGICH								
Yes	220	136	84	0.111	214	206	8	1
No	12	10	2		11	11	0	

Note: Statistics: Chi-square test; Age was expressed as mean and examined by t-test; WT: wild-type; MU: mutation-type; MetS: metabolic syndrome; TG: fasting triglyceride; T2DM: type 2 diabetes mellitus; HBP: hypertension; Cigarette: cigarette smoking habit; FGICH: family gastrointestinal cancer history.

Table 2: Basic characteristic according to KRAS/NRAS status of colorectal cancer in patients of both genders.

Factors	Female		P	Male		P	Female		P	Male		P
	wKRAS	mKRAS		wKRAS	mKRAS		wNRAS	mNRAS		wNRAS	mNRAS	
MetS												
No	46	30	0.833	76	38	0.186	70	3	1	107	4	1
Yes	12	7		12	11		18	1		22	0	
BMI												
<25	41	28	0.838	63	35	0.819	64	2	0.244	91	4	0.575
≥25	13	8		23	14		19	2		36	0	
T2DM												
No	50	29	0.32	80	36	0.007	73	3	0.541	109	4	1
Yes	8	8		8	13		15	1		20	0	
TG												
< 1.7	50	29	0.32	59	34	0.778	72	4	1	89	1	0.099
≥ 1.7	8	8		29	15		16	0		40	3	
Low-HDL												
No	29	25	0.09	54	28	0.629	50	2	1	77	3	1
Yes	29	12		34	21		38	2		52	1	
HBP												
No	34	21	0.858	44	25	0.909	51	2	1	66	2	1
Yes	24	16		44	24		37	2		63	2	
Cigarette												
No				44	31	0.121				72	0	0.042
Yes				44	18					57	4	
FGICH												
Yes	53	36	0.399	83	48	0.42	82	4	1	124	4	1
No	5	1		5	1		6	0		5	0	

Note: Statistics: Chi-square test; wKRAS: wild-type KRAS; mKRAS: mutation-type KRAS; wNRAS: wild-type NRAS; mNRAS: mutation-type NRAS.

Association between T2DM and KRAS Mutation of CRC in Patients of Different Gender

To further determine whether there was any sex-specific difference for the association between T2DM and KRAS mutation, we examined the relationship of KRAS mutation and T2DM in CRC patients of both gender. Univariately, T2DM significantly associated with KRAS mutation in overall patients (OR=2.63, 95% CI: 1.28-5.37, P=0.008) and male patients (OR=3.61, 95% CI: 1.38-9.47, P=0.009), but not in female patients. Multivariate logistic analysis including other potential confounders such as age, high BMI (≥25), low HDL, high TG (≥ 1.7), cigarette smoking habit, and family gastrointestinal carcinoma history, retained the above significance (Table 3). The results further demonstrated T2DM was an independent risk factor for KRAS mutation in CRC patients, especially in male patients (Table 4).

Table 3: Association between type 2 diabetes and mutation of KRAS and KRAS/NRAS of colorectal cancer in overall patient or both sex.

Factors (subgroup)	Variables	Univariate		Multivariate	
		OR (95% CI)	P	OR (95% CI)	P
Mut-KRAS (Male)	T2DM	3.61 (1.38-9.47)	0.009	3.17 (1.17-8.61)	0.024
	BMI≥25			1.08 (0.47-2.52)	0.852
	Low HDL			1.06 (0.50-2.23)	0.887
	TG ≥ 1.7			0.92 (0.41-2.05)	0.831
	Cigarette			0.59 (0.28-1.23)	0.16
	FGICH			0.40 (0.04-3.75)	0.423
	Age			1.01 (0.97-1.04)	0.744
Mut-KRAS (Female)	T2DM	1.72 (0.58-5.08)	0.324	2.54 (0.69-9.29)	0.16
	BMI≥25			0.71 (0.23-2.14)	0.538
	Low HDL			0.41 (0.14-1.17)	0.095
	TG ≥ 1.7			1.85 (0.58-5.93)	0.302
	FGICH			0.25 (0.03-2.52)	0.242
	Age			1.01 (0.97-1.04)	0.788
Mut-KRAS (Overall)	T2DM	2.63 (1.28-5.37)	0.008	2.61 (1.21-5.60)	0.014
	BMI≥25			0.92 (0.48-1.76)	0.805
	Low HDL			0.74 (0.41-1.34)	0.322
	TG ≥ 1.7			1.11 (0.58-2.13)	0.753
	Cigarette			0.58 (0.28-1.21)	0.145
	FGICH			0.33 (0.07-1.57)	0.163
	Male			1.04 (0.54-1.99	0.915
	Age			1.01 (0.98-1.03)	0.66

Note: Statistics: binomial logistic regression.

Table 4: Association between type 2 diabetes and KRAS mutation features of colorectal cancer.

KRAS mutation type	Overall	Non-T2DM	T2DM	P
Female				
Non-mutation	58	50	8	0.645
34G>T	18	14	4	
34G>A	2	2	0	
34G>C	2	2	0	
35G>T	6	4	2	
35G>A	9	7	2	
Male				
Non-mutation	88	80	8	0.023
34G>T	24	19	5	
34G>A	4	3	1	
34G>C	1	1	0	
35G>T	4	4	0	
35G>A	10	6	4	
38G>A	6	3	3	
Overall				
Non-mutation	146	130	16	0.043
34G>T	42	33	9	

34G>A	6	5	1	
34G>C	3	3	0	
35G>T	10	8	2	
35G>A	19	13	6	
38G>A	6	3	3	

Note: Statistics: Chi-square test; T2DM: type 2 diabetes; wKRAS: wild-type KRAS; mKRAS: mutant KRAS

Association between Mutation of KRAS or KRAS/NRAS and Pathological Features of CRC

To study the association between mutation of KRAS or KRAS/NRAS and pathological features of CRC, we examined the relationship between mutation of KRAS or KRAS/NRAS and pathological features including pathological subtypes and histological grade of CRC. As showed in Table 5, the rates of mucinous adenocarcinoma and adenocarcinoma with components (mucinous or signet-ring cell) in KRAS mutation group were 11.6% (10/86), 9.3% (8/86), which is higher than corresponding rates of KRAS wild-type group [4.1% (6/146), 4.8% (7/146), P=0.026]. Meanwhile, the rate of mucinous carcinoma in KRAS/NRAS-mutation group was significantly higher than KRAS/NRAS-wild-type group [12.8% (12/94) vs. 4.6% (6/131), P=0.026]. However, KRAS mutation was not significantly associated with histological grade in the present study (P> 0.05). The results indicated RAS mutation to be associated with mucinous histological phenotype of CRC which might lead to adverse clinical outcome.

Table 5: Association between KRAS/NRAS status and pathological features of colorectal cancer.

Pathology	KRAS status		P	NRAS status		P	KRAS/NRAS status		P
	WT	MU		WT	MU		WT	MU	
Mucinous CA									
No	137	76	0.143	201	6	0.127	125	82	0.026
Yes	9	10		16	2		6	12	
Subtypes									
Classic AC	130	68	0.026	188	5	0.155	120	73	0.029
MAC	6	10		15	1		5	11	
SRCC	3	0		1	1		1	1	
Components	7	8		13	1		5	9	
High grade									
No	95	57	0.379				87	60	0.579
Yes	42	19					38	22	

Note: Statistics: Chi-square test; WT: wild-type; MU: mutation-type; CA: carcinoma; Classic AC: classic adenocarcinoma; MAC: mucinous adenocarcinoma; Components: adenocarcinoma with mucinous and/or signet-ring cell components.

Discussion

There are a few reports about the association between diabetes and KRAS mutation so far and the results are inconclusive [16,17]. A recent study showed a tendency of positive association between abnormal HbA1C [≥48 mmol/mol (6.5%), the cut-off for diagnosis of T2DM] and KRAS mutation of CRC, although the association was not statistically significant (OR=1.85, P=0.1, n=170) [16]. Our results indicated T2DM predicted risk of mutation of KRAS, especially for men, while other assessed factors such as MetS, high BMI, low HDL, hypertension and hypertriglycemia did not significantly associated with status of KRAS mutation. The reason for the difference between above reports and our present results may partly due to the different criteria for T2DM. It is interesting that the association between T2DM and KRAS mutation of CRC was stronger in men in comparison with women. Previous studies have revealed a significant association between T2DM and CRC in men, but only a weak or unremarkable association with women [1,18]. Colon cancer risk is increased in prediabetic men, but not in women [19].

The present results demonstrated T2DM was significantly associated with mutation of KRAS in men, but only a weaker association between T2DM and KRAS mutation in women. The reason for the gender difference of diabetic impact may partly attributed to the different levels of sex hormone or its related factors such as adiponectin and sex hormone binding globulin (SHBG) [20]. Adiponectin is a kind of hormones secreted by adipose tissue and exerts an insulin-sensitizing effect [21]. Adiponectin was considered to play a role in colorectal carcinogenesis in men [22]. Low levels of adiponectin are associated with obesity, T2DM and increased risk of KRAS-mutant CRC [23]. Previous study demonstrated adiponectin level in male is significantly lower than female [24]. Moreover, lower levels of adiponectin and SHBG were likely to be correlated with family T2DM history-associated risk of CRC in male [25]. Further study is needed to clarify the molecular mechanism for the gender impact on association among T2DM and KRAS mutation, biological behaviors of CRC.

Although the mechanism for the association between T2DM and KRAS mutation is not fully understood so far, several lines of evidence may partly contribute to the association between T2DM and KRAS mutation status of CRC. At first, high level of glucose (in T2DM condition) promotes mutagenesis in human lymphoblastoid cells [26]. Secondly, high level of glucose triggers nucleotide imbalance through O-GlcNAcylation of key enzymes and induces KRAS mutation in pancreatic cells [27]. Whether these mechanisms are involved T2DM-associated mutation of KRAS of needs further investigation. KRAS mutation was considered to be associated with aggressive pathological features and prognosis of CRC [28,29]. Oncogenic KRAS can drive invasion and metastasis in a mouse model of CRC and the TGF-beta pathway was revealed as a key mediator for mutated KRAS-driven invasiveness [30]. Our present data showed of KRAS mutation to be significantly associated with mucinous phenotype of CRC (MAC or AC with mucinous components). Recent studies suggested KRAS mutation to be associated with risk of colorectal mucinous carcinoma and gastric mucinous carcinoma [7,9,31]. Because mucinous adenocarcinoma is commonly more aggressive than classic CRC, T2DM-associated KRAS-mutation might influence progression and prognosis via promoting mucinous phenotype of CRC.

Another interesting finding of the present study is the significant association between cigarette smoking and increased frequency of NRAS mutation in CRC. Although previous studies suggested cigarette smoking might be a risk factor for KRAS mutation-negative CRC, these studies did not assess the NRAS status of CRC in the meantime [32,33]. Although our present data also showed the KRAS mutation rate of CRC in male patients with cigarette smoking habit was lower than non-smoking patients, the NRAS mutation rate in male smoking patients was significantly higher than non-smoking patients. The results support the notion that cigarette smoking was a risk factor for NRAS mutation in CRC. This study has some limitations. It was a single center clinical research and the samples for KRAS/NRAS mutation evaluation were relative limited. The mutation rates of NRAS is very low and hardly to analyze its subgroups.

Conclusion

In summary, the present study suggested T2DM to be significantly associated with risk of KRAS mutation of CRC, especially for male patients. KRAS/NRAS mutation was associated with mucinous phenotype of CRC. Cigarette smoking might be a risk factor for NRAS mutation of CRC in men. T2DM might influence carcinogenesis, progression and prognosis of CRC by promoting KRAS mutation and mucinous phenotype.

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Statement of Conflict of Interest

None declared.

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