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ORIGINAL ARTICLE

Higher Expression of Proteins in IGF/IR Axes in Colorectal Cancer is Associated with Type 2 Diabetes Mellitus

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Abstract Preexisting type 2 diabetes mellitus (preDM) increases occurrence and mortality of colorectal cancer (CRC). Insulin growth factor (IGF)/insulin receptor (IR) axes play an important role in the development of both diabetes and CRC. We aimed to explore the characteristics of proteins expression in IGF/IR axes in CRC tissues with preDM. Two hundred fifty CRC patients in West China hospital were included in analysis. Among them, 125 patients had history of diabetes matched by 125 CRC without diabetes at a 1:1 ratio. Immunohistochemical staining was used to detect the expression of proteins in IGF/IR axis. More positive expression of IGF-1, IGF-1R and IR were found in CRC group with diabetes than in non-diabetes group. No difference was detected in the expression of IR substrate-1, IR substrate-2, IGF-2, IGF binding protein 3, and mammalian target of rapamycin between two groups. Multivariate analysis showed that diabetes history was associated with all of the expression of IGF-1, IGF-1R and IR, and higher T staging and lymph node metastasis were respectively independent factors of IGF-1 and IGF-1R expression in CRC patients. Besides, IGF-1 expression was positively associated with IGF-1R and IR expression in all CRC tissues, and the association of IGF-1 and IR expression seemed to be closer in diabetes group than in non-diabetes group. Higher expression of IGF-1, IGF-1R and IR proteins in CRC was associated with diabetes, suggesting IGF-1/IR signaling may play a special part in development of CRC in patients with diabetes.

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Introduction

Cancer and diabetes mellitus are prevalent diseases with great impact on health worldwide. From accumulating epidemiologic evidence, type 2 diabetes mellitus (T2DM) influences occurrence and mortality of some malignancies, e.g. breast cancer, lung cancer, colorectal cancer (CRC), pancreatic cancer, etc. [1, 2]. CRC is the second leading cause of cancer death in the world. Evidences indicated that preexisting diabetes mellitus (preDM) increased the risk and cancer-specific mortality of CRC [3–5], but decreased disease-free survival and overall survival of CRC patients [6], and among patients receiving curative surgery for early colon cancer, DM is a predictor of poor prognosis [7]. Moreover, metformin use appears to be associated with a reduced risk of developing CRC among diabetic patients and induces an improved survival outcome in patients with CRC and diabetes [8–10]. Increasing evidences showed that CRC was associated with diabetes, but the pathological mechanisms underlying the relationship between CRC and T2DM before CRC diagnosis are less apparent. In type 2 diabetes, insulin resistance may lead to very high serum insulin levels and indirectly an increase in the bioactivity of IGF-1 by inhibiting IGF binding proteins, resulting in an increased mitogenic activity [1], and actually, increased insulin, IGF-I and IGF-II levels are associated with tumor growth [11]. Hyperinsulinemia, insulin resistance and tumor pathogenesis simultaneously involve the imbalance of IGF /insulin pathways, more likely to be the potential mechanism. As we found previously, higher expression of IGF-1R and IRS-2 proteins were observed in NSCLC patients

with preexisting T2DM, which suggested that IGF signaling may be involved in development of NSCLC associated with diabetes [12]. In this study, we conducted an immunohistochemical analysis of molecules in IGF /insulin axis in CRC with or without preDM, so as to investigate the potential molecules which play roles in mechanism that diabetes affects CRC.

Materials and Methods

Patients and Tissue Sample

The data of colorectal cancer patients who were admitted in West China Hospital of Sichuan University during January 2009 to November 2011 was reviewed. Those with preDM and underwent radical surgical removal for local diseases were extracted from the database. Patients with insufficient clinical and/or pathological data or concurrent other malignancies were excluded, and those received radiotherapy or chemotherapy before surgery were also excuded. Finally, 125 CRC patients with preDM had been confirmed in analytic group.

For comparison with CRC with preDM, we matched CRC patients without the diagnosis of diabetes from the database at a 1:1 ratio on gender, age (± 3 years), pathological type, tumor differentiation and the pTNM stage of cancers. The matched CRC patients without diabetes should also be confirmed to have their morning fasting blood glucose lower than 5.9 mmol/L during their admission for surgery. The resected tumor specimens were acquired from formalin-fixed and paraffin-embedded pathological samples from pathology department. Clinicopathological characteristics of all included patients were collected. The study was approved by the Biomedical Ethics Committee of West China Hospital, Sichuan University, China. Informed consent from every patient included was received.

Immunohistochemical Staining

The tissue samples of CRC were cut into sections of 4 μm mounted on silanized slides. All of the sections processed through deparaffin and hydrous procedures, and heated for 7 min at high fire via microwave to retrieve in sodium citrate buffer (pH 6.0). Then the sections were incubated with the rabbit polyclonal antibodies at 4 °C overnight, which were purchased from Abcam, Hong Kong, China: IGF-2 (clone ab9574), IGF 1 receptor (IGF-1R, clone ab131476) and insulin receptor substrate 1 (IRS-1, clone ab52167) at 1:100; IGF-1 (clone ab9572) at 1:75; IR (clone ab5500), IRS-2 (clone ab46811) at 1:50 and mTOR (clone ab2732); and IGFBP3 (clone ab76001) at 1:20, respectively. Subsequently, the sections were treated with PV6001 Two-Step immunohistochemistry Detection Reagent (ZSJQ-BIO, Bei Jing, China) for 1 h at 37 °C. 3,3'-diaminobenzidine color fixing and commercial hematoxylin contrastaining were performed.

Evaluation of Immunohistochemical Staining Results

Each sample was examined in a high power field at 200 times magnification and chosen five fields to evaluate. Immunostaining was classified based on staining intensity and percentage of positive tumor cells. Staining intensity was determined as 0 (absent), 1 (weak), 2 (moderate), 3 (strong). Expression level of the antigens was semi-quantified using an immunohistochemistry score (range, 0–300) calculated by multiplying staining intensity with the percentage of positive tumor cells. The immunoreactivity was classified: 0, score ≤ 60; 1+, 60 < score ≤ 140; 2+, 140 < score ≤ 220; 3+, 220 < score ≤ 300. Patients with an immunohistochemistry score of ≤60 were considered as negative and those with a score of >60 as positive, which will be used for the subsequent multivariate analysis. All slides were evaluated and scored independently by one investigator who was blind to clinical information of the subjects.

Statistical Analysis

Chi-square test was used for comparison between clinicopathological characteristics and antigens expression of two groups. Rank correlation was used to analyze the association between different proteins' expression. Binary logistic regression analysis was used to adjust for multiple potential confounders, including gender, age, location, hypertension history, T staging, lymph node metastasis, tumor differentiation, CEA and/or T2DM history to determine whether the clinicopathological variables were jointly associated with expression of the antigens. A p-value of <0.05 was considered statistically significant. Statistical analysis was performed using SPSS 17.0.

Results

Clinicopathological Characteristics

The clincopathological characteristics of 125 included and paired patients are shown in Table 1. The gender, and pathological type were paired in all patients between two groups. Age difference between two groups was not over 3 years and the stages were matched at 99.2 %. Relatively, in the group with diabetes, patients are usually older

Table 1 Clinicopathological characteristics of the CRC patients with DM and paired patients without DM

	With DM (n = 125)	Without DM (n = 125)	P-value
Male:Female	76:49 (125)	76:49 (125)	1.00
Median age, years (range)	67.0 (41–91)	68.6 (42–89)	0.81
Location			1.00
Colon	53 (42.4 %)	53 ((42.4 %))	
Right colon	20 (16.0 %)	28 (22.4 %)	
Transverse colon	4 (3.2 %)	4 (3.2 %)	
Left colon	9 (7.2 %)	4 (3.2 %)	
Sigmoid colon	20 (16.0 %)	17 (13.6 %)	
Rectum	72 (57.6 %)	72 (57.6 %)	
Tumor differentiation			0.69
Well	4 (3.2 %)	4 (3.2 %)	
Moderate	85 (68.0 %)	91 (72.8 %)	
Poor	36 (28.8 %)	30 (24.0 %)	
T staging			0.99
pT1	6 (4.8 %)	5 (4.0 %)	
pT2	23 (18.4 %)	24 (19.2 %)	
pT3	69 (55.2 %)	68 (54.4 %)	
pT4	27 (21.6 %)	28 (22.4 %)	
Lymph node metastasis			0.97
pN0	66 (52.8 %)	66 (52.8 %)	
pN1	48 (38.4 %)	47 (37.6 %)	
pN2	11 (8.8 %)	12 (9.6 %)	
Distant metastasis			1.00
pM0	124 (99.2 %)	124 (99.2 %)	
pM1	1 (0.8 %)	1 (0.8 %)	
pTNM Stage			1.00
I	23 (18.4 %)	23 (18.4 %)	
II	43 (34.4 %)	42 (33.6 %)	
III	58 (46.4 %)	59 (47.2 %)	
IV	1 (0.8 %)	1 (0.8 %)	

CRC colorectal cancer, *DM* diabetes mellitus

(median age at 67), having more poorly and moderately differentiated cancer (96.8 %), with a higher proportion of cancer at T3–4 (76.8 %).

Expression Characteristics of the Proteins in the IGF/IR System in CRC

The expressions of IGF-1, IGF-2, IRS-1 and IRS-2, mTOR were mainly located in the cytoplasm of malignant cells in CRC tissues with positive rates of 54.8 %, 81.6 %, 56.8 %, 25.2 %. IGFBP3 expression were found in 61.2 % of samples mostly in the cytoplasm and very few in the nucleus. Most of the CRC tissues were found to overexpress IGF1R and IR at 65.2 % and 56.4 % in the cell membrane and cytoplasm. The representative pictures of these molecules expression in CRC were shown in Fig. 1.

Expression Differences of the Proteins in the IGF/IR System between Groups with or without T2DM

IGF-1 staining in the group with preDM was observed to be more positive than that in the group without diabetes (P = 0.031); IGF-1R staining was also more positive in the preDM group than group without diabetes (P = 0.012). Similarly, IR staining was found more positive in the group with preDM than group without diabetes (P = 0.015). No statistically significant differences were found in the expression of IGF-2, IGFBP3, IRS-1, IRS-2 and mTOR between CRC with or without preDM, as shown in Table 2.

The Correlation of Clinicopathological Factors with Expression of the Proteins in the IGF/IR System in CRC

The age and gender of patients, tumor location, T staging, histological differentiation, lymph node metastasis, CEA, history of hypertension, history of T2DM were included as main covariates for multivariate analysis to identify the potential association factors with expression of IGF-1, IGF-1R and IR in 250 patients with CRC. Diabetes history was associated with IGF-1 positive expression. And location in colon, pT3 ~ 4, increasied CEA level were also independent factors to associate with more IGF-1 positive expression. Then, we found that both diabetes history and lymph node metastasis were the independent factor associating with IGF-1R positive expression. Similarly, diabetes history was associated with IR positive expression without other significant factors (Table 3).

The Correlation between IGF-1, IGF-1R, IR Expression

Rank correlation was employed to analyze the association between the graded expressions of IGF-1, IGF-1R, and IR (0, 1+, 2+, 3+). IGF-1 expression was positively associated with IGF-1R and IR expression in CRC respectively, while no statistically significant correlation was found between IGF-1R and IR. Similar results were found in CRC group with and without diabetes, but the association of IGF-1 and IR expression seemed to be closer in the group with diabetes (r_s = 0.34, P < 0.0001) than in the group without diabetes (r_s = 0.19, P = 0.038) (Table 4).

Discussion

In this study, we found that a majority of the proteins in IGF-1R/IR axes were highly expressed in CRC tissues, except for

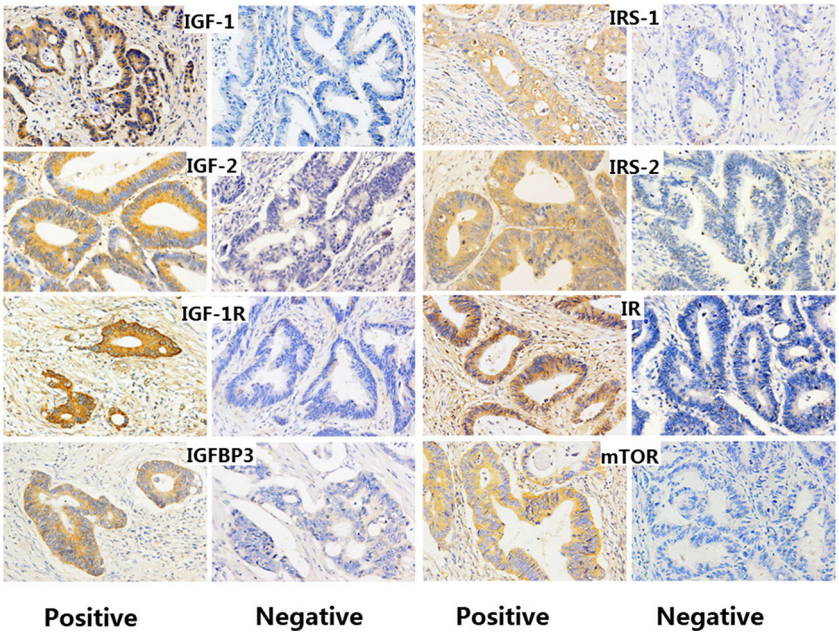

Fig. 1 The representative figures of expression of the proteins in CRC (×200)

IRS-2, suggesting that IGF-1R/IR signaling might be involved in CRC development. Moreover, we matched both CRC patients with and without diabetes on main factors, finding that proteins expression in IGF/IR axes, such as IGF-1, IGF-1R, IR, were of more positive numbers in CRC group with preDM than in the group without preDM. Similarly, Multivariate analysis confirmed that history of diabetes was respectively associated with IGF-1, IGF-1R, IR positive expression in all included subjects with CRC, illuminating that there might be potential difference in mechanism of CRC development in patients with preDM.

Table 2 The expression differences of proteins in IGF/IR signaling pathway between CRC with and without DM

	DM	Negative	Positive	*P*-value
IGF-1	+	58 (46.4 %)	67 (53.6 %)	0.03
	−	75 (60.0 %)	50 (40.0 %)	
IGF-2	+	23 (18.4 %)	102 (81.6 %)	1.00
	−	23 (18.4 %)	102 (81.6 %)	
IGFBP3	+	48 (38.4 %)	77 (61.2 %)	0.90
	−	49 (39.2 %)	76 (60.8 %)	
IGF-1R	+	34 (27.2 %)	91 (72.8 %)	0.01
	−	53 (42.4 %)	72 (57.6 %)	
IR	+	45 (36.0 %)	80 (64.0 %)	0.02
	−	64 (51.2 %)	61 (48.8 %)	
IRS-1	+	55 (44.0 %)	70 (56.0 %)	0.80
	−	53 (42.4 %)	72 (57.6 %)	
IRS-2	+	89 (71.2 %)	36 (28.8 %)	0.19
	−	98 (78.4 %)	27 (21.6 %)	
mTOR	+	59 (47.2 %)	66 (52.8 %)	0.31
	−	67 (53.6 %)	58 (46.4 %)	

CRC colorectal cancer, *DM* diabetes mellitus, *IGF-1* insulin growth factor-1, *IGF-2* insulin growth factor-2, *IGFBP3* insulin growth factor binding protein 3, *IGF-1R* insulin growth factor − 1 receptor, *IR* insulin receptor, *IRS-1* insulin receptor substrate-1, *IRS-2* insulin receptor substrate-2, *mTOR* mammalian target of rapamycin

IGFs and its receptors were observed to overexpress in many cancers, including CRC [13, 14]. Blockade or down-regulation of IR and IGF-1R were respectively associated with reduced tumor growth [15, 16]. IGFs can play a paracrine and/or autocrine role in promoting tumor growth, binding of IGFs to IR, IGF-1R, and hybrid receptors resulting in recruitment of IRS-1 to IRS-4 and other proteins and then activation of PI3K/AKT and RAS/MAPK pathways is critically involved in CRC carcinogenesis- proliferation, migration, metastasis and survival [17, 18]. Our study found more positive expression of IGF-1, IR and IGF-1R in the group with diabetes and history of diabetes was associated with positive expression of those proteins. Several lines of evidence suggest that the insulin-like effects of IGF-1 interacting with associated receptors, such as IGF-1R, IR or hybrid receptors, play an important role in the maintenance of normal glucose homeostasis and etiopathogenesis of type 2 diabetes [19]. In hyperinsulinemic states, higher insulin levels may influence cancer development through upregulating IR expresson, increasing hepatic IGF-I production and/or indirectly enhance bioactivity of IGF-1 by decreasing IGFBPs level [19]. And prospective epidemiological studies and meta-analyses comfirmed higher IGF-I levels increased the risk of colorectal cancer [20]. In animal experiments, higher levels of insulin and IGF-I was associated with the increased growth of transplanted lung and colon cancer cells at the condition of induced obesity and insulin resistance

Table 3 Correlation of the IGF-1/IGF-1R expression and clinicopathological factors in 250 patients with CRC

	IGF-1			IGF-1R			IR		
	Odds ratio	95 % CI	*P*-Value	Odds ratio	95 % CI	*P*-Value	Odds ratio	95 % CI	*P*-Value
Age (year)	1.00	0.38–1.16	0.94	1.00	0.97–1.03	0.83	0.99	0.96–1.02	0.52
Gender									
Male vs. Female	0.15	0.38–1.16	0.66	1.19	0.68–2.05	0.56	1.07	0.63–1.82	0.80
Location									
Colon vs. Rectum	1.77	1.01–3.12	0.047	1.66	0.96–2.88	0.07	1.01	0.57–1.80	0.97
T staging									
pT3-pT4 vs. pT1-pT2	2.70	1.31–5.58	0.007	1.07	0.53–2.17	0.86	1.70	0.93–3.09	0.08
Lymph node metastasis									
Present vs. absent	1.15	0.65–2.03	0.64	1.75	1.02–3.00	0.04	0.98	0.57–1.68	0.93
Tumor differentiation									
Moderate to well vs. poor	0.60	0.32–1.10	0.10	1.28	0.69–2.39	0.44	1.08	0.60–1.95	0.81
CEA									
Increased vs. normal	0.47	0.27–0.82	0.007	1.41	0.82–2.42	0.22	0.65	0.38–1.10	0.10
Hypertension									
Present vs. absent	1.46	0.80–2.65	0.22	0.84	0.46–1.56	0.59	1.43	0.80–2.57	0.23
History of diabetes									
Present vs. absent	1.96	1.15–3.37	0.01	2.08	1.21–3.56	0.008	1.88	1.13–3.10	0.02

Positive expression vs. negative expression

CRC colorectal cancer, *DM* diabetes mellitus, *NDM* non-diabetes mellitus, *IGF-1* insulin growth factor-1, *IGF-1R* insulin growth factor − 1 receptor, *IR* insulin receptor

[21]. With insulin medication for diabetes patients, studies show that insulin-resistant individuals administrated chronically by high doses of insulin might potentially stimulate cell proliferation by signaling through IR and IGF-IR [11]. In accord with Furgeson's observation [22], activation of the IR/IGF-1R contributed to the increased growth of mammary tumors. Therefore, in our study, IGF/IR signaling may participate in the development of colorectal cancer associated with diabetes.

Besides, we also found that location in colon, higher T stage and increased CEA level were respectively associated with more positive expression of IGF-1 in CRC tissues. Several studies observed that IGF-1 was correlated with malignant characteristics of cancer in human and mice. For example, a previous study found that tumor size and depth of invasion were significantly associated with IGF-1 expression in CRC tissues [23]. And in the liver-specific IGF-I deficiency model of colon cancer, administration of IGF-I not only increased tumor growth, but also led to the development of neovascularization and metastases [24]. Consequently, we speculated that signaling activation of IGF-1 via relevant receptors is one of possible mechanisms of CRC development. Next, we also found in CRC that IGF-1R expression was more positive in those with lymph nodes metastasis, along with our finding in IGF-1, which illustrates that IGF/IGF-1R axis may function in progression of CRC. Similarly, strong IGF-1R positivity was reported to correlate with higher grade and higher-stage tumors suggesting an increased number of IGF-

Table 4 Correlation between the IGF-1, IGF-1R and IR expression

	All CRC population (*N* = 250)				DM (*N* = 125)				NDM (*N* = 125)			
	IGF-1		IGF-1R		IGF-1		IGF-1R		IGF-1		IGF-1R	
	r_s	*P*-value	r_s	*P*-value	r_s	*P*-value	r_s	*P*-value	r_s	*P*-value	r_s	*P*-value
IGF-1R	0.31	<0.0001	–	–	0.27	0.003	–	–	0.31	<0.0001	–	–
IR	0.19	0.003	−0.02	0.70	0.34	<0.0001	0.10	0.27	0.19	0.04	−0.02	0.79

Graded expression (0, 1+, 2+, 3+)

CRC colorectal cancer, *IGF-1* insulin growth factor-1, *IGF-1R* insulin growth factor-1 receptor, *IR* insulin receptor

1R receptors may favor the metastasis of colorectal cancer [25].

Through rank correlation analysis, expression level of IGF-1 was found to be positively associated with that of IGF-1R and IR, respectively. IGF-I, as a more potent mitogen, links to IGF-1R regulating cancer cell proliferation, invasion, and metastasis with stronger anti-apoptotic activity than insulin [26] which has stronger metabolic activity [27]. According to the insulin receptor isoform present (IR-A and IR-B), those hybrid receptors including IR-A strongly bind to insulin and IGF-2, whereas these IR-B isoform hybrid receptors represent a possible signaling pathway for the insulin-like effects of IGF-I [19]. Actually, it was suggested that the binding of IGF-I with these hybrid receptors may stimulate glucose uptake just as insulin does binding with its receptor [28]. Similar results were found in diabetes group with closer correlation between IGF-1 and IR. Therefore, in those with preDM, signaling through IGF-1R might lead to more mitogenic effects than signaling through IR, which activates the metabolic signaling pathway.

With immunohistochemistry to analyze molecule expression in IGF/IR axis in CRC with preDM, our research is one of the preliminary explorations of IGF/IR signaling in cancer development with diabetes. Lack of data analysis of diabetes medication was the drawback of this study. However, in non-small cell lung cancer and breast cancer with diabetes, enhanced expression of IGF-1R was observed and made difference in cancer process [13, 29], which impels us further to investigate the role of this pathway in carcinogenesis associated with diabetes. Meanwhile, we are carrying on prospective experiments for verification.

Conclusion

Our study found higher expression of IGF-1, IGF-1R and IR proteins in CRC patients with preDM, and diabetes was independently associated with the expression of IGF-1, IGF-1R, and IR, suggesting that IGF-1/IR signaling may play an special part in development of CRC in patients with diabetes. Additional investigations should be considered.

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Compliance with Ethical Standards

Conflict of Interest The author(s) declare that they have no competing interests.

Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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