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Circulating soluble receptor for advanced glycation end products and other factors in type 2 diabetes patients with colorectal cancer

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Abstract

Background: Recent study showed that individuals with type 2 diabetes have a high risk of developing colorectal cancer (CRC), in which Receptor for Advanced Glycation End Products (RAGE) plays a pivotal role. We conducted a cross-sectional study to examine the relationships of circulating sRAGE, CRC and other clinical factors in type2 diabetes patients.

Methods: A total of 150 type 2 diabetes patients aged 50 years and older were enrolled, including 50 patients with CRC and 100 patients without CRC. We measured Serum levels of sRAGE and interleukin-6(IL-6) using an enzyme-linked immunosorbent assay (ELISA). In addition, other clinical parameters were also measured during hospitalization.

Results: Type 2 diabetes patients with CRC had higher triglyceride, total cholesterol, IL-6, and circulating sRAGE levels and lower use of medicines than type 2 diabetes patients without CRC. Circulating sRAGE was associated with an increased risk for CRC (OR = 2.289 for each SD increase in sRAGE, 95% CI = 1.037–5.051; $P = 0.04$) among Type 2 diabetes patients after adjustment for confounders. Furthermore, circulating sRAGE levels among type 2 diabetes patients were positively correlated with triglyceride ($r = 0.377$, $P < 0.001$), total cholesterol ($r = 0.491$, $P < 0.001$), and low-density lipoprotein cholesterol (LDL-c)($r = 0.330$, $P < 0.001$) levels; the homeostatic model assessment for insulin resistance(HOMA-IR)score ($r = 0.194$, $P = 0.017$); and fasting serum insulin ($r = 0.167$, $P = 0.041$) and IL-6 ($r = 0.311$, $P < 0.001$) concentrations.

Conclusions: Our results suggested that circulating sRAGE is independently risk factor for CRC, and also closely related to inflammation, dyslipidemia in type 2 diabetes patients.

Keywords: Type 2 diabetes, Colorectal Cancer, Soluble receptor for advanced glycation end-products

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Background

CRC is the third most commonly diagnosed cancer and the second leading cause of cancer death, accounting for 10.2% of the total diagnosed cancer and 9.2% of the cancer death [1]. Multiple risk factors of colorectal cancer, including sedentary lifestyle, obesity and a western-style diet,are closely related to diabetes [2, 3]. Diabetes in adults are becoming increasingly common all over the world, with number of 451 million in 2017 and this number is evaluated to increase to 693 million by 2045 [4]. Several studies have previously reported that individuals with type 2 diabetes have a higher risk of developing CRC than their nondiabetic counterparts [5–8]. Therefore, it's important to understand the potential pathogenetic links between these two diseases.

The receptor for advanced glycation end products (RAGE) is a multiligand, transmembrane cell surface receptor belonging to the immunoglobulin superfamily [9]; major ligands for RAGE are advanced glycation end products (AGEs), high-mobility group box 1 (HMGB1), S100/calgranulins and amyloid-beta [10]. Binding of RAGE to its ligands can activate chronic inflammatory conditions and create a microenvironment that strongly contributes to tumor development [11, 12]. In our recent study, we demonstrated that AGE–RAGE signaling enhanced HCT116 CRC cell proliferation, in which AGE–RAGE-mediated carbohydrate responsive element binding protein (ChREBP) induction played an important role [13]. In addition to the membrane-bound isoform of RAGE, several soluble forms of RAGE (sRAGE) appear in circulating, generated by endogenous secretory major splice variant of RAGE (esRAGE) or proteolytic cleavage of the cell-bound receptor (cRAGE) [14, 15]. sRAGE binding to RAGE ligands cannot trigger a signaling cascade because it has no transmembrane and intracellular domains. For this reason, sRAGE is thought to play a beneficial role by acting as an invalid receptor that attenuates RAGE-ligand interactions at the cell surface [16]. However, the circulating sRAGE concentrations are too low to capture and eliminate AGEs in diabetes patients [17]. Accumulating evidence has shown that increased levels of circulating sRAGE can as one potential marker for the expression of RAGE and activation of the RAGE axis, resulting many adverse outcomes in diabetes patients [17–19]. Therefore, we hypothesized that type 2 diabetes patients with higher circulating sRAGE are at a higher risk of developing CRC.

In this cross-sectional study, we focused on exploring the relationships between circulating sRAGE levels and CRC and other clinical factors in type 2 diabetes patients, with the aim to find out potential therapeutic interventions for reducing occurrence and progression of CRC in type2 diabetes patients.

Methods

Subjects

The participants were hospitalized in the Endocrinology or Colorectal Surgery inpatient department of Xinhua Hospital Affiliated with Shanghai Jiaotong University School of Medicine between October 2016 and January 2018. Informed consent was obtained from all participants. All enrolled subjects had type 2 diabetes aged 50 years and older and type 2 diabetes was diagnosed according to the 1999 World Health Organization criteria. Patients with CRC were diagnosed by histopathology for the first time and without any treatment for CRC. Patients were excluded based on the following criteria: a history of cancer, inflammatory bowel disease, severe cardiovascular disease, chronic renal insufficiency, severe liver dysfunction, a family history of CRC and previous CRC diagnosis. Finally, 150 patients were selected and divided into two groups: 50 diabetes patients (33 men and 17 women) with histologically proven CRC for the first time were divided into the type 2 diabetes patients with CRC group, and the other 100 diabetes patients (54 men and 46 women) without CRC were divided into the type 2 diabetes patients without CRC group. The study was approved by the Ethics Committee of Xinhua Hospital Affiliated with Shanghai Jiaotong University School of Medicine.

Measurement of circulating sRAGE, IL-6, and other clinical indicators

All serum samples of eligible study subjects were obtained in a fasted state. Serum samples for sRAGE and IL-6 analysis were stored at − 80 °C until analysis. Circulating sRAGE and IL-6 were detected with enzyme-linked immunosorbent assay (ELISA) kits (Human sRAGE Quantikine and Human IL-6 Valukine; R&D Systems, Minneapolis, MN) in duplicate according to the manufacturer's recommendations. For the ELIS As, the inter-assay coefficient of variation (CV) was 4–10%, and the intra-assay CV was 3–9%.Blood insulin and C-peptide concentrations were assayed by an automated analyzer (ADVIA Centaur XP, Siemens, Berlin, Germany). Hemoglobin A1c (HbA1c) was determined by high-performance liquid chromatography (BIO-RAD VARIANT II, California, USA). Blood glucose and lipid levels were measured with an autoanalyzer (Hitachi 7600, Tokyo, Japan). Height and body weight were measured, body mass index (BMI kg/m^2) and homeostatic model assessment for insulin resistance (HOMA-IR) were calculated. The current and past medical histories, personal backgrounds and chronic diabetic complications of all participants were investigated by trained physicians during the hospitalization.

Statistical analyses

The results are expressed as the means ± SDs for normally distributed variables and as medians (interquartile ranges) for nonnormally distributed variables. Categorical variables were expressed as percentages. Data with normal distributions and homoscedasticity were analyzed by Student's t test, and those with non-normal distributions or heteroscedasticity were analyzed by the Wilcoxon rank sum test. The χ^2 test was used for categorical variables. We examined the correlation between circulating sRAGE levels and the study variables using Pearson correlation analysis for normally distributed variables and Spearman rank correlation analysis for nonnormally distributed variables. To investigate the associations between circulating sRAGE concentrations and CRC, multivariable adjusted logistic regression analyses were performed to assess the OR for CRC. The variable circulating sRAGE was standardized for the logistic regression analysis. Statistical analyses were performed in SPSS version 22 (IBM Corp, Armonk, NY, USA). A two-sided p value of < 0.05 was considered to indicate significance.

Results

Characteristics of enrolled patients

Table 1 shows the demographic and clinical characteristics of enrolled type 2 diabetes patients with and without CRC. There were no significant differences between the groups in terms of sex, age, duration of diabetes, BMI, LDL-c level, HDL-c level, HOMA-IR level, fasting plasma glucose level, fasting C-peptide level, fasting serum insulin level, hemoglobin A1c percentage, percentage of current smokers and use of sulfonylurea (all $P > 0.05$). Compared with control participants, type 2 diabetes patients with CRC had significantly higher triglyceride, total cholesterol, IL-6, and circulating sRAGE levels, and a lower proportion of these patients used medicines, including insulin, metformin, thiazolidinedione, a-glucosidase inhibitors, NSAIDs and statins (all $P < 0.05$).

The relationship between sRAGE levels and other clinical factors

The circulating sRAGE level was significantly and positively correlated with triglyceride, total cholesterol, and

Table 1 Characteristics of type 2 diabetes patients with and without CRC

	T2D with CRC	T2D without CRC	*p*
Number of patients	50	100	–
Sex (male %)	66	54	0.160
Age (yr)	69.44 ± 7.73	67.29 ± 7.83	0.114
Duration of diabetes (yr)	11.50 (5.00–15.00)	10.00 (6.00–18.00)	0.743
BMI (kg/m2)	24.70 ± 2.04	25.25 ± 3.21	0.205
TG (mmol/L)	1.98 (1.64–2.33)	1.65 (1.08–2.30)	0.028
TC (mmol/L)	4.78 (4.33–5.04)	4.33 (3.43–4.98)	0.013
LDL-c (mmol/L)	2.64 ± 0.58	2.42 ± 0.83	0.061
HDL-c (mmol/L)	1.16 ± 0.40	1.16 ± 0.27	0.957
HOMA-IR	3.93 (2.43–5.46)	3.66 (1.75–5.61)	0.539
Fasting plasma glucose (mmol/L)	7.41 (5.92–9.47)	7.73 (6.27–9.37)	0.534
Fasting C-peptide (nmol/L)	0.83 (0.66–1.06)	0.74 (0.51–1.05)	0.096
Fasting serum insulin (pmol/L)	83.48 (63.47–109.38)	72.43 (43.22–100.78)	0.191
Hemoglobin A1c (%)	8.09 ± 0.79	8.47 ± 1.77	0.071
IL-6 (ng/L)	78.70 (58.23–114.17)	24.49 (14.00–36.05)	<0.001
sRAGE (ng/L)	604.61 ± 210.21	404.80 ± 166.18	<0.001
Current smoker (%)	26	15	0.103
Insulin use (%)	34	84	<0.001
Sulfonylurea use (%)	32	45	0.127
Metformin use (%)	16	83	<0.001
Thiazolidinedione use (%)	0	13	0.018
a-Glucosidase inhibitor use (%)	12	62	<0.001
NSAID use (%)	8	41	<0.001
Statin use (%)	6	40	<0.001

Student's t test, the Wilcoxon rank sum test, or the χ^2 test was used to test for significant differences. *BMI* body mass index, *TG* triglycerides, *TC* total cholesterol, *LDL-c* low-density lipoprotein cholesterol, *HDL-c* high-density lipoprotein cholesterol, *HOMA-IR* homeostatic model assessment for insulin resistance, *IL-6* interleukin-6, *sRAGE* soluble receptor for advanced glycation end products

LDL-c levels; the HOMA-IR score; and fasting serum insulin and IL-6 levels ($r = 0.377$, $r = 0.491$, $r = 0.330$, $r = 0.194$, $r = 0.167$, and $r = 0.311$, respectively; all $P < 0.05$). The circulating sRAGE level was not significantly correlated with age, the duration of diabetes, BMI, or the levels of HDL-c, fasting plasma glucose, fasting C-peptide or hemoglobin A1c (all $P > 0.05$) (Table 2).

Influences of medicine use on circulating sRAGE concentration

Figure 1 shows the influence of different medicines on the circulating sRAGE concentration. Type 2 diabetes patients treated with insulin showed lower circulating sRAGE levels than type 2 diabetes patients not treated with insulin (429.87 ± 185.19 versus 557.03 ± 217.32 ng/L, $P < 0.001$). Type 2 diabetes patients treated with metformin showed lower circulating sRAGE levels than type 2 diabetes patients not treated with metformin (419.87 ± 177.00 versus 550.90 ± 219.55 ng/L, $P < 0.001$), and type 2 diabetes patients treated with a-glucosidase inhibitors showed lower circulating sRAGE levels than type 2 diabetes patients not treated with a-glucosidase inhibitor (420.11 ± 167.05 versus 513.94 ± 223.13 ng/L, $p = 0.005$). The use of sulfonylurea, thiazolidinedione, NSAIDs and statins did not significantly influence circulating sRAGE levels ($P > 0.05$ for all).

The risk of CRC associated with increased circulating sRAGE levels

Table 3 shows that for subjects with a 1-SD increase in the circulating sRAGE level, the OR for CRC was increased (OR = 2.289; 95% CI = 1.037–5.051; $P = 0.04$) after adjustment for age; sex, BMI, smoking status, HOMA-IR score, and the levels of triglycerides, total cholesterol, LDL-c, HDL-c, and IL-6.

Table 2 Correlations of sRAGE and other clinical parameters in the study subjects

	r	p
Age (yr)	0.072	0.380
Duration of diabetes (yr)	−0.144	0.079
BMI (kg/m2)	0.001	0.992
TG (mmol/L)	0.377	<0.001
TC (mmol/L)	0.491	<0.001
LDL-c (mmol/L)	0.330	<0.001
HDL-c (mmol/L)	0.048	0.558
HOMA-IR	0.194	0.017
Fasting plasma glucose (mmol/L)	0.142	0.083
Fasting C-peptide (nmol/L)	0.110	0.181
Fasting serum insulin (pmol/L)	0.167	0.041
Hemoglobin A1c (%)	0.053	0.519
IL-6 (ng/L)	0.311	<0.001

Discussion

Our study of type 2 diabetes patients indicated that higher circulating sRAGE levels were significantly associated with an increased risk of CRC. Moreover, increased circulating sRAGE levels were significantly correlated with increased triglyceride, total cholesterol, LDL-c, fasting serum insulin, and IL-6 levels and HOMA-IR scores. Type 2 diabetes patients treated with insulin, metformin and a-glucosidase inhibitors showed lower circulating sRAGE levels than Type 2 diabetes patients not treated with these agents.

RAGE was recently reported to be highly expressed in CRC tissues and to be closely associated with invasion, metastasis, and angiogenesis in CRC [20, 21]. In this study, we found that the circulating sRAGE level was notably increased in type 2 diabetes patients with CRC. Regression analysis further indicated that an elevated level of circulating sRAGE was independently associated with an increased incidence of CRC in type 2 diabetes patients. Higher level of circulating sRAGR contribute to higher risk of developing CRC mainly related to activation of RAGE axis. RAGE interacts with diverse ligands and activates multiple signaling pathways, which are the main contributors to the development of malignancies. The major RAGE axis-related and underlying molecular mechanisms inducing CRC in patients with type 2 diabetes may include the following: 1) AGE–RAGE interaction promotes the activation of multiple signaling cascades, including the NADPH oxidase, Jak/Stat, and MAPK cascades, resulting in the activation of transcription factors, such as nuclear factor kB (NF-kB), or IFN-stimulated response elements (ISRE), which are involved in proliferation, metastasis, tumor generation [22]. 2) The S100P-RAGE interaction stimulates signaling pathways such as the MAPK, NF-kB, and PI3K/Akt pathways, which are closely related to proliferation and angiogenesis [23, 24]. 3) The HMGB1-RAGE interaction activates signaling pathways, including the K-Ras, MAPK and NF-Kb pathways, which are closely related to inflammation and cancer [25–29]. In addition, RAGE can directly stimulate some proximal signaling events related to cancer [30]. Thus, RAGE plays a vital role in the development of CRC in type 2 diabetes patients through a complex process.

Our results indicate that type 2 diabetes patients with CRC had significantly higher IL-6 levels than controls, revealing associations between IL-6 levels and CRC. Consistent with this result, accumulating evidence indicates that higher IL-6 concentrations are associated with a higher risk for CRC development [31, 32]. As a proinflammatory cytokine, IL-6, along with IL-6 signaling, is

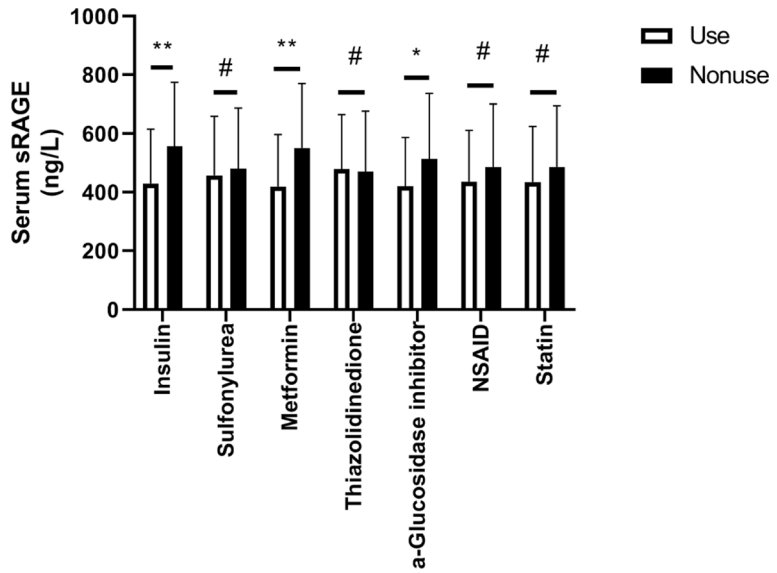

Fig. 1 Circulating sRAGE concentration in groups using or not using different drugs. *$p<0.05$, **$p<0.001$, #$p>0.05$

closely related to the initiation and progression of the CRC-associated inflammatory microenvironment [33, 34]. Previous studies reported that IL-6 mediates the promotion of tumorigenesis by mainly activating the JAK/STAT3 signaling pathway [35–37]. We also found that circulating sRAGE was positively correlated with IL-6 and that a 1-SD increase in the circulating sRAGE level was associated with a 2.29-fold increase in CRC risk, regardless of the IL-6 level. Consistent with this result, a previous study reported that RAGE signaling pathways can upregulate the expression of important cytokines, including IL-6; and that these cytokines and their respective receptors trigger multiple signaling pathways, resulting in the production of large amounts of proinflammatory mediators and RAGE in a positive feed-forward loop [12]. Both RAGE and IL-6 play vital roles in linking cancer with inflammation through multiple signaling pathways [12]. Thus, measurement of circulating sRAGE and IL-6 level can aid the prediction and/or diagnosis of CRC in middle-aged and older type 2 diabetes patients.

Table 3 Risk of CRC associated with a 1-SD increase in the circulating sRAGE level

	OR (95% CI)	*P*
Model 1	3.331 (2.075–5.347)	<0.001
Model 2	3.603 (2.089–6.217)	<0.001
Model 3	3.609 (2.081–6.257)	<0.001
Model 4	2.289 (1.037–5.051)	0.040

OR odds ratio, *CI* confidence interval. We assigned the value of 0 to participants without CRC and assigned the value of 1 to those with CRC. Model 1 was adjusted for age, sex, BMI and smoking status. Model 2 was further adjusted for triglyceride, total cholesterol, LDL-c, and HDL-c levels based on model 1. Model 3 was further adjusted for the HOMA-IR score based on model 2. Model 4 was further adjusted for IL-6 levels based on model 3.

Our results indicate that type 2 diabetes patients with CRC had significantly higher triglyceride and total cholesterol levels than controls, consistent with previous studies reporting that total cholesterol and triglycerides increase the risk of CRC [38, 39]. Although the mechanism underlying the links between total cholesterol and triglycerides and CRC has not been completely clarified, several potential mechanisms have been proposed. The association between triglycerides and CRC may be ascribed to bile acid excretion or the energy supply to neoplastic cells [40]. Furthermore, as the major components of dyslipidemia, total cholesterol and triglycerides are linked to chronic inflammation [41], oxidative stress [42], and insulin resistance [43], all of which are associated with neoplastic processes. In addition, dyslipidemia and CRC have common environmental risk factors, such as Western eating patterns, alcohol use, obesity, and low physical activity levels [40]. In our study, we found that the levels of both cholesterol and triglycerides were positively correlated with the circulating sRAGE level, suggesting that the roles of cholesterol and triglycerides in inducing the development of CRC may be mediated through the RAGE signaling pathway. Further studies are required to better understand the role of dyslipidemia in CRC.

Various antidiabetes agents have different influences on colorectal carcinogenesis. Among these medicines, metformin, a-glucosidase inhibitors and insulin have received the most attention all the time. In patients with diabetes, treatment with metformin and a-glucosidase inhibitors is associated with a reduced risk of developing

CRC [44, 45], whereas insulin has been shown to promote CRC [46]. In our study, we found that type 2 diabetes patients treated with insulin, metformin or a-glucosidase inhibitors had lower circulating sRAGE levels than patients not treated with these agents and that type 2 diabetes patients with CRC had lower rates of medicine use, including insulin, metformin, a-glucosidase inhibitors, thiazolidinedione, NSAIDs and statins, suggesting that insulin, metformin and a-glucosidase inhibitors may protect against CRC mediated by RAGE. The potential reason that the results of our study differ from those of previous research is that the hypoglycemic effect of insulin plays a greater role than its proliferative effect in these type 2 diabetes patients with CRC, whose glucose was poorly managed, as reflected by the lower use of most kinds of diabetes medicines. Our results suggest that diabetes management is very important for Type 2 diabetes patients to reduce chronic complications, including CRC.

To our knowledge, this is the first study specifically aimed at exploring the relationships among circulating sRAGE concentrations, CRC and clinical factors in type 2 diabetes patients. However, several limitations should be addressed. First, a cause-effect relationship cannot be inferred because of the cross-sectional nature of this study. Second, information about the cancer stages, tumor sites and histopathological outcomes of the patients with CRC was insufficient. Including these assessments may improve the strength of future studies. Third, since the subjects were recruited from a single center in China, the study population may not represent the general population.

Conclusions

In conclusion, our results suggested that circulating sRAGE is independently risk factor for CRC, and also closely related to inflammation, dyslipidemia in type 2 diabetes patients. Therapeutic interventions that reduce RAGE levels or RAGE axis activity deserve further investigation.

Abbreviations

CRC: colorectal cancer; sRAGE: Soluble Receptor for Advanced Glycation End Products; ChREBP: Carbohydrate responsive element binding protein; BMI: Body mass index; TG: Triglycerides; TC: Total cholesterol; LDL-c: Low-density lipoprotein cholesterol; HDL-c: High-density lipoprotein cholesterol; HOMA-IR: Homeostatic model assessment for insulin resistance; IL-6: Interleukin-6

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Authors' contributions

XHZ, NL, and MJZ designed the study. YA, XHZ, XLW, HBC, BL,PD and QS recruited the subjects, processed samples, and contributed to the acquisition of data. XHZ and HBC analyzed the data. XHZ wrote the manuscript. HBC, BL, PD and QS revised the manuscript. All authors have read and approved the final manuscript.

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Availability of data and materials

The data that support the findings of this study are available from the corresponding author on reasonable request. Inquiries for data access may be sent to the following e-mail address: chenhanbei@xinhuamed.com.cn

Ethics approval and consent to participate

All procedures performed in this study involving human participants have been approved by the Ethics Committee of the Xinhua Hospital Affiliated to Shanghai Jiaotong University School of Medicine and performed in accordance with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Written informed consent was obtained from all the respondents.

Consent for publication

This manuscript does not report personal data such as individual details, images or videos; therefore, consent for publication is not applicable.

Competing interests

All authors declare that they have no competing interests.

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