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Original Article

Effects of Insulin Pathway on Glucose and Lipid Metabolism Disorder in Different Pathological Types of Colorectal Adenomas

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Abstract

Background and Aims: To explore how insulin resistance promotes colorectal adenomas by disrupting the balance of glucose and lipid metabolism.

Methods: All the clinical data were collected for retrospective analysis were divided into five groups. Clinical chemical analysis was run by automatic biochemical analyzer. An enzyme-linked immunosorbent assay was used to detect peripheral blood insulin levels, and RT-qPCR was used to detect mRNA expression of insulin pathway-related genes, including *INSR*, *KCNJ11*, and *PIK3CA*). Moreover, the expression levels of all genes were also obtained from the GEO database and compared.

Results: In the adenoma groups, only TG, HDL-C levels, and HOMA-IR scores were statistically increased comparing the control group, but TC was statistically different among the adenoma groups. Chi-square results showed that the presence of fatty liver increased adenoma generation and progression, and the ROC curve revealed that HOMA-IR scores had high diagnostic value for progressive and non-progressive adenomas. Gene analysis showed that *INSR*, *KCNJ11*, and *PIK3CA* all had a significantly lower expression in colorectal adenocarcinoma tissues compared with the control group. GEO bioinformatics analysis revealed that *INSR* was statistically increased in the GSE 37364 dataset, and *PIK3CA* was significantly different between adenoma and controls in the GSE 41657 dataset, while *KCNJ11* was elevated when comparing colorectal carcinoma to controls in the GSE 41657 dataset.

Conclusions: Through clinical pathological data analysis, bioinformatics mining, and molecular biology experiments, *INSR*, *KCNJ11*, and *PIK3CA* were shown to act on colorectal adenomas through the insulin resistance pathway and may be used as distinguished potential biomarkers for tumorigenesis.

Keywords: Insulin resistance; Colorectal tumor; Glucose metabolic disorder; Lipid metabolic disorder.

Abbreviations: AUC, area under the curve; BMI, body mass index; CRC, colorectal carcinoma; ELISA, enzyme-linked immunosorbent assay; GEO, Gene Expression Omnibus; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment-insulin resistant; *INSR*, insulin receptor gene; *KCNJ11*, potassium inwardly rectifying channel subfamily J member 11 gene; LDL-C, low density lipoprotein cholesterol; *PIK3CA*, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha gene; ROC, receiver operating characteristic; TC, total cholesterol; TG, triglyceride.

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Introduction

In 2020, there were 19.29 million patients newly diagnosed with cancer in the world and 4.57 million of these patients were in China, which accounted for 23.70% of the global incidence. There were 9.96 million cancer-related deaths worldwide, including 3 million in China, which accounts for approximately 30% of all cancer-related deaths. As such, China has become one of the top ten countries in terms of the incidence of cancer and cancer-related deaths. In 2020, the incidence of colorectal cancer (CRC) in China was 560,000, with 290,000 deaths, and both of these values are among the highest in China's cancer incidence and mortality

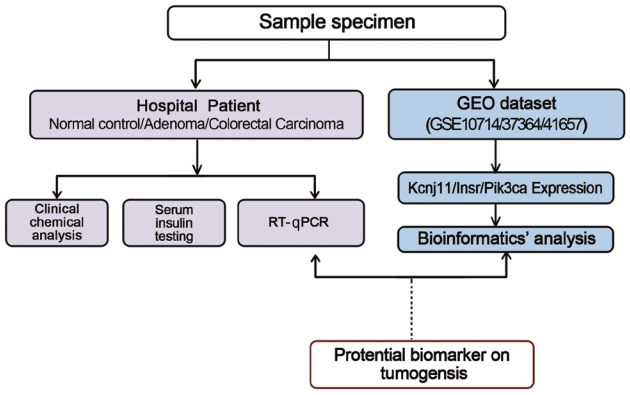

Fig. 1. Flow chart of experimental design.

rates.[1,2] According to previous studies, the possible underlying mechanisms of CRC may be associated with insulin resistance and hyperglycemia.[3,4] Colorectal adenoma is a noncancerous precursor of CRC, and most CRCs evolve from colorectal adenomas.[5,6]

There is only one step between advanced adenoma and CRC, so it has attracted much attention. However, the exact etiology and pathogenesis of advanced colorectal adenomas are still unclear. Epidemiological investigations have shown that lifestyle, diet, obesity, and other factors are closely related to colorectal adenomas, but there are not many related studies.[7] It is unknown if abnormal glucose and lipid metabolism are related to different pathological types of colorectal adenomas, and if they may influence the progression of colorectal adenomas.

Insulin resistance refers to a reduction in the body's responsiveness or sensitivity to the physiological effects of insulin. Clinical studies have found that approximately 25% of the normal population has insulin resistance.[8] In 1995, Stem proposed the "common soil" theory, which suggested that insulin resistance is the common basis for diseases such as diabetes and lipid metabolism disorders.[9] Therefore, this study aimed to explore how insulin resistance promotes the occurrence and development of colorectal adenomas by disrupting the balance of glucose and lipid metabolism.

Materials and methods

Research object and study design

A retrospective analysis was conducted on patients who underwent a colonoscopy at the Affiliated Hospital of Chengde Medical University from September 2017 to January 2020, and data of patients with blood lipid test results were included (Fig. 1). All clinical investigators followed the Ethical Principles for Medical Research Involving Human Subjects outlined in the Declaration of Helsinki, and amended by the World Medical Association.[10] All included patients gave their oral and written informed consent. The study was approved by the Ethics Committee of the Affiliated Hospital of Chengde Medical University (reference number LL2021009).

Colorectal polyps removed by colonoscopy were divided into two parts: one was placed in liquid nitrogen, and the other was placed in a 10% formaldehyde solution and sent to the pathology department. Samples that were confirmed to be an adenoma by histopathological examination were included in the adenoma group. The diagnosis by the pathologist classified colorectal adenomas into one of three groups: low-grade tubular adenomas (34 cases, diameter < 1 cm,number 1–7), low-grade villous adenomas (13 cases), or high-grade intraepithelial neoplasia (20 cases). Patients with no obvious abnormalities by endoscopy during the same period were included in the control group. In all groups, patients with a history of CRC, colorectal surgery, malignant tumors, and recent use of drugs affecting blood lipids were excluded. At the same time, data concerning patient height, weight, blood pressure, and body mass index (BMI) were collected.

The patients with a colorectal adenoma included in the experimental group were also placed into one of two groups, advanced adenomas (13 cases of low-grade villous adenoma and 20 cases of high-grade intraepithelial neoplasia) or non-advanced adenoma (34 cases of low-grade tubular adenoma), according to the 2006 U.S. "Guidelines for Follow-up after Colorectal Polypectomy".[11]

Clinical chemical analysis

After collecting peripheral venous blood from patients, the AU5800 (Beckman, USA) automatic biochemical analyzer was used to detect fasting blood lipids and blood glucose levels. Blood lipids included total cholesterol (TC), triglyceride (TG), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C).

Ultrasound examination

The patients all underwent an ultrasound examination of the liver in the ultrasound department to assess the potential presence of fatty liver.

Serum insulin testing

The commercial enzyme-linked immunosorbent assay (ELISA) kit (Beyotime Biotechnology, Shanghai, China) was used to detect serum insulin levels in all groups, and homeostasis model assessment-insulin resistant (HOMA-IR) scores were calculated using the following formula: HOMA-IR = fasting blood glucose level (mmol/L) × fasting insulin level (mU/L)/22.5.

Reverse transcription quantitative polymerase chain reaction (RT-qPCR) method to detect related genes

A commercial RNA extraction kit (Tiangen Biotechnology Co. Ltd., Beijing, China) was used to extract total RNA from adenoma tissue, and a spectrophotometer (Thermo Scientific, Ultra Trace) was used to measure RNA concentration and purity. Primers for three genes, *INSR* (insulin receptor), *KCNJ11* (potassium inwardly rectifying channel subfamily J member 11), and *PIK3CA* (phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha), were designed using the National Center for Biotechnology Information (NCBI) website (Table 1). The BioRad PCR machine was used for reverse transcription and PCR amplification in a single step.

Bioinformatics analysis

Several datasets (GSE10714, GSE37364, and GSE41657) with gene expression (*KCNJ11, INSR*, *PIK3CA*) in normal colon (NC), adenoma (A), and CRC samples were downloaded from the Gene

Table 1. Names, accession numbers, and primer sequences used in the study

	Accession number	Left sequence	Right sequence
KCNJ11	NM_031358	5′-CTACTTCAGGCAAAACTCTG-3′	5′-GAACTTTCCAATATTTCTTTT-3′
INSR	NM_017071	5′-AGCTGGAGGAGTCTTCAT-3′	5′-AAGGGATCTTCGCTTT-3′
PIK3CA	NM_133399	5′-CAAGGATCTGACTTATTTCC-3′	5′-CTAACCATGCTGTTACCAA-3′
*ACTB**	NM_001101	5′-GATCATTGCTCCTCCTGAGC-3′	5′-GGGAAAAGCCATGC-3′

*Housekeeping gene β-actin. INSR, insulin receptor; KCNJ11, potassium inwardly rectifying channel subfamily J member 11; PIK3CA, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha.

Expression Omnibus (GEO) database (http://www.ncbi.nlm.nih.gov/geo). In total, there were: seven CRC, five adenoma, and three normal mucosa specimens in the GSE10714 dataset; 27 CRC, 29 adenoma, and 38 normal mucosa samples in the GSE37364 dataset; and 25 CRC, 51 adenoma, and 12 normal mucosa specimens in the GSE 41657 database. All the three genes (*KCNJ11, INSR*, *PIK3CA*) from each profile were analyzed using the Assistant for Clinical Bioinformatics website (https://www.aclbi.com/).

Statistical analysis

All statistical analyses were automatically performed using SPSSAU (Beijing, China). Analyses of measurement data were carried out with analysis of variance (ANOVA) tests, stepwise regression analysis, and categorical data were analyzed using the chi-square test and the chi-square test for trends. The receiver operating characteristic (ROC) curve was drawn on SPSSAU website.

Results

Baseline Characteristics

There were 62 cases in the control group (36 males, 26 females; average age 52.87 ± 12.23 years), 34 cases in the high-grade tubular adenoma group (23 males, 11 females; average age 53.32 ± 13.37 years), 13 cases in the high-grade villous adenoma group (nine males, four females; average age 51.15 ± 15.10 years), and 20 patients in the high-grade intraepithelial neoplasia group (including tubular and villous; 11 males, nine females; average age 53.10 ± 13.07 years).

One-way ANOVAs were used to determine the differences between pathological types for BMI and age. As presented in Table 2, samples from different pathological types all showed consistency in BMI and age ($p > 0.05$). The chi-square test showed that the control group and the adenoma groups were also consistent for gender, and there was no statistical difference ($\chi^2 = 1.53$, $p > 0.68$).

Blood lipid levels

For TC, TG, HDL-C, and LDL-C levels, normality tests were carried out. TG and HDL-C levels did not have normality characteristics, but TC and LDL-C did. The ANOVA revealed that LDL-C had uniform variance, and the one-way ANOVA revealed that there was a significant difference between the control group and each experimental group ($p < 0.01$; Table 2). TC was analyzed with a Brown-Forsythe test, and there is no statistical difference between the control group and each experimental group ($p = 0.10$). However, there were statistical differences among the three experimental groups ($p = 0.04$; Table 2). TG and HDL-C levels were analyzed using the Kruskal-Wallis non-parametric test, and there were statistical differences between the control and experimental groups ($p = 0.001$); but there was no statistical difference among the three experimental groups, and only TG showed a significant difference ($p < 0.05$; Table 3).

HOMA-IR

The Kruskal-Wallis test was used to analyze the control group and different pathological types of samples and revealed significant differences in HOMA-IR scores ($p < 0.05$; Table 3, Fig. 2).

Fatty liver and hypertension

The specimens were divided into two groups according to fatty liver and hypertension indicators. Chi-square results revealed that blood pressure was not significant ($\chi^2 = 7.70$, $p > 0.05$). However, each group had a significant difference for fatty liver ($\chi^2 = 11.50$, $p < 0.01$). According to the difference in percentage comparison, the

Table 2. Blood lipid levels and BMI values of experimental groups and control group

	Pathology type (mean ± standard deviation)				*F/Brown F**	*P*,***
	Normal control (*n* = 62)	Low-grade tubular adenoma (*n* = 34)	Low-grade villous adenoma (*n* = 13)	High-grade intraepithelial neoplasia (*n* = 20)		
LDL-C	3.08 ± 0.97	2.56 ± 1.06	3.42 ± 0.81	3.87 ± 1.30	7.15	0.00**
BMI	24.99 ± 2.54	24.84 ± 2.61	25.33 ± 2.68	25.89 ± 2.81	0.784	0.51
Age	52.87 ± 12.33	53.32 ± 13.57	51.15 ± 15.72	53.10 ± 13.41	0.09	0.97
TC	4.31 ± 2.05	4.25 ± 0.95	4.45 ± 1.35	5.22 ± 1.50	2.23	0.10
	/	4.25 ± 0.95	4.45 ± 1.35	5.22 ± 1.50	3.47	0.04*

*$p < 0.05$; **$p < 0.01$. LDL-C, low-density lipoprotein cholesterol; MBI, Body Mass Index.

Table 3. Blood lipid levels and HOMA-IR score analysis of experimental group and control group

	Pathology type, Median M (P25, P75)				Kruskal-Wallis H value	*p*
	Normal control (*n* = 62)	Low grade tubular adenoma (*n* = 34)	Low-grade villous adenoma (*n* = 13)	High-grade intraepithelial neoplasia (*n* = 20)		
HDL	1.21 (0.80, 1.70)	1.58 (1.20, 2.00)	1.59 (1.20, 1.80)	2.02 (1.40, 2.50)	15.82	0.001**
	NA	1.58 (1.20, 2.00)	1.59 (1.20, 1.80)	2.02 (1.40, 2.50)	2.88	0.24
TG	1.36 (1.00, 2.00)	1.56 (1.30, 2.00)	1.64 (1.40, 1.80)	2.12 (1.60, 3.20)	15.67	0.001**
	NA	1.56 (1.30, 2.00)	1.64 (1.40, 1.80)	2.12 (1.60, 3.20)	8.78	0.01*
HOMA-IR	3.05 (1.70, 3.90)	0.58 (0.50, 0.60)	0.68 (0.50, 0.80)	0.69 (0.60, 0.90)	94.19	0.00**
	NA	0.58 (0.50, 0.60)	0.68 (0.50, 0.80)	0.69 (0.60, 0.90)	11.66	0.003**

*$p < 0.05$; **$p < 0.01$. TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment-insulin resistant.

proportion of normal controls without fatty liver was 70.97%; the proportion of high-grade intraepithelial neoplasia with fatty liver was 70.00%; and the proportion of low-grade villous adenomas with fatty liver was 53.85%.

Correlation between clinical features and pathological types

TC, TG, HDL-C, LDL-C, BMI, HOMA-IR scores, presence of fatty liver, hypertension, gender, and age were used as independent variables, and the control group and adenoma subgroups were used as dependent variables for a stepwise regression analysis. The model was automatically recognized, and finally there were six final items in the model, including TG, HDL-C, LDL-C, BMI, HOMA-IR, and fatty liver. The R^2 value was 0.61, which suggested that TG, HDL-C, LDL-C, BMI, HOMA-IR scores, and fatty liver could explain 61.4% of the changes from healthy individuals to adenomas. According to an F test ($F = 32.32$, $p = 0.00 < 0.05$), the model was effective. To further analyze the influence of the above independent variables on colorectal adenomas of different pathological types, the three groups of adenomas were used as dependent variables to perform a stepwise regression analysis. After the model was automatically identified, the remaining five items included TG, HDL-C, LDL-C, HOMA-IR scores, and gender. In the model, the R-square value was 0.49, which indicated that TG, HDL-C, LDL-C, HOMA-IR scores, and gender could explain 49.0% of the changes between the three groups of adenomas. This model also passed the F test ($F = 11.72$, $p = 0.00 < 0.05$), indicating that the model was effective. After regrouping the adenomas into only two groups, non-advanced and advanced, only BMI had a significantly positive influence on the grouping relationship ($t = 4.57$, $p = 0.00 < 0.01$), and HOMA-IR produced a significantly negative impact relationship ($t = -14.23$, $p = 0.00 < 0.01$).

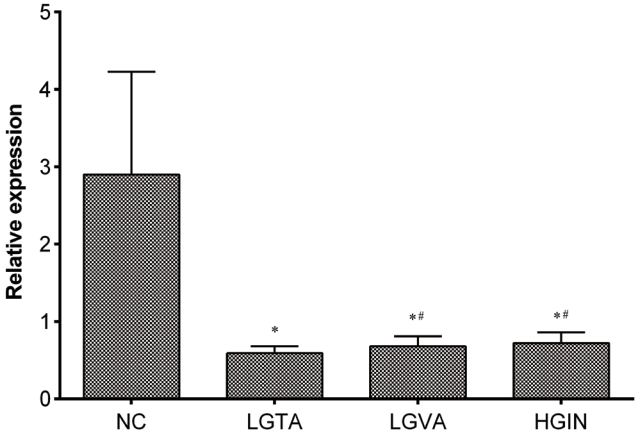

Fig. 2. Homeostasis model assessment-insulin resistant (HOMA-IR) index expression in different groups. NC, normal control; LGTA, low-grade tubular adenoma; LGVA, low-grade villous adenoma; HGIN, high-grade intraepithelial neoplasia. * *vs* NC; # *vs* LGTA.

ROC curve

A total of two ROC curves were constructed for BMI and HOMA-IR to determine the diagnostic value of progressive adenomas and non-progressive adenomas in pathological subtypes. First, the "gold standard" was set, and the low-level villous adenoma and high-grade intraepithelial neoplasia were used as the cut-off point and set as positive, and low-grade tubular adenoma was set as negative. The ROC curves for BMI and HOMA-IR scores were drawn to predict the progression of adenomas, and the area under the curve (AUC) was determined to compare its prediction sensitivity. The positive ratio was 49.25% and the negative ratio was 50.75%. The AUC value corresponding to BMI was 0.58, indicating that the diagnostic value of BMI for progressive and non-progressive colorectal adenomas was relatively low. The AUC value corresponding to insulin-resistance was 0.74 (95% confidence interval: 61.72–85.69%), indicating that insulin-resistance had a high diagnostic value for progressive and non-progressive adenomas (Table 4).

Gene expression

The RT-qPCR Gene Analyzer was used to analyze the mRNA expression of insulin pathway-related genes (*INSR*, *KCNJ11*, and *PIK3CA*), and *ACTB* (β-actin) was used as the housekeeping gene. Compared to the control group, *PIK3CA* was significantly lower in the colorectal adenoma groups with different pathological types

Table 4. ROC curves

	AUC	SD	*p*	95% CI
BMI	0.58	0.07	0.25	0.44–0.72
Insulin resistance	0.74	0.06	0.00**	0.62–0.86

**$p < 0.01$. MBI, Body Mass Index.

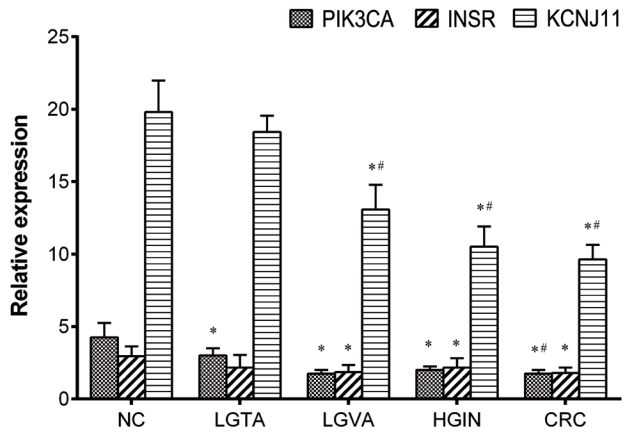

Fig. 3. Colonic mRNA expression levels of *INSR*, *KCNJ11*, and *PIK3CA* in different experimental groups. NC, normal control; LGTA, low-grade tubular adenoma; LGVA, low-grade villous adenoma; HGIN, high-grade intraepithelial neoplasia; CRC, colorectal carcinoma. * *vs* NC; # *vs* LGTA. INSR, insulin receptor; KCNJ11, potassium inwardly rectifying channel subfamily J member 11; PIK3CA, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha.

($p < 0.05$), and *KCNJ11* as well as *INSR* were only significant in low-grade villous adenoma and high-grade intraepithelial neoplasia compared with the low-grade tubular adenoma group. *KCNJ11* was also significantly decreased in low-grade villous adenoma and high-grade intraepithelial neoplasia. *INSR*, *KCNJ11*, and *PIK3CA* all have low expression in colorectal adenocarcinoma tissues, and there were significant differences compared to the control group. At the same time, *KCNJ11* and *PIK3CA* were also significantly different from the low-grade tubular adenoma group comparing with control group. (Fig. 3).

Bioinformatics analysis

The GEO database bioinformatics analysis revealed that in the GSE 37364 dataset, the insulin pathway-related gene *INSR* was statistically decreased in the CRC and A groups compared to the NC group. In the GSE 41657 dataset, *PIK3CA* was significantly increased in group A compared to group NC, while *KCNJ11* was elevated in group A when compared to groups CRC and NC. However, there was so significant difference between all three genes (*INSR*, *KCNJ11*, and *PIK3CA*) in GSE 10714 (Fig. 4).

Discussion

Colorectal adenomas are benign tumors of the intestine that originate from the glandular epithelium of the colorectal mucosa. They are also a precancerous disease closely related to the occurrence of CRC. Colorectal adenomas can be classified into tubular adenomas, villous adenomas, and villous tubular adenomas, according to pathological characteristics.[12] Tubular adenomas account for 70% of colorectal adenomas, and the malignancy rate is generally less than 20%, while villous gland tumors have a relatively high malignant transformation rate, normally > 30%.[13] Therefore, villous adenomas are classified as advanced adenomas whether they are well-differentiated or poorly differentiated, and poorly differentiated tubular adenomas less than 10 mm are classified as non-advanced adenomas. The statistical analysis of the baseline clinical data of this study found that blood lipid levels, BMI, HOMA-IR, and fatty liver have a certain relationship with the occurrence of adenomas, which is consistent with current literature that suggests obesity, fatty liver, hyperlipidemia, and metabolic syndrome such as hyperglycemia, may be risk factors for CRC and advanced adenomas.[7] However, when the grade was adjusted and the three groups of colorectal adenoma patients classified into either advanced or non-advanced adenomas, only BMI and HOMA-IR scores appeared to influence the occurrence and development of CRC tumors. This finding was interesting and important since advanced adenoma is only one step away from cancer, although advanced adenoma does not cause obvious harm to the human body whereas CRC ranks second in the world for cancer-related deaths, and the data presented in the current study discovered that the insulin pathway with *INSR*, *KCNJ11*, and *PIK3CA* acts on colorectal adenomas to promote the progression from adenoma to advanced adenoma.

At present, many countries are vigorously promoting the "CRC screening program", which includes endoscopy, fecal occult blood test, etc., in anticipation of reducing the incidence and mortality of CRC.[14,15] Under normal circumstances, it takes more than ten years for low-grade adenomas to progress to high-grade adenomas and eventually into cancer, but often people are cured through endoscopic resection after adenomas are found. However, we cannot ignore the potential harm causing by advanced adenomas, and the existing data are not complete enough for patients to stop all further treatment after the adenoma is removed.[16] Our findings showed that disorders of glucose and lipid metabolism affect the progression of advanced adenomas, so the analysis of colorectal adenomas becomes extremely important.

Insulin is an anabolic hormone that plays a vital role in switching between glucose and lipid metabolism. In a healthy state with normal insulin metabolism, humans can effectively transform from carbohydrate metabolism to fat metabolism, thereby maintaining a balance of glucose and lipid metabolism.[17,18] Wanda Foltyn and colleagues tested the plasma glucose, insulin, and insulin resistance levels in 88 controls and 82 CRC patients and found that plasma insulin and insulin resistance play a role in the susceptibility of CRC (especially rectal cancer).[19] After constructing ROC curves for BMI and HOMA-IR, we found that HOMA-IR scores correspond to an AUC value of 0.737, indicating that HOMA-IR has a higher diagnostic value for progressive and non-progressive adenomas. Therefore, the pathway that affects insulin resistance may alter adenoma progression. Molecular and animal-level studies indicate that hyperinsulinemia plays a vital role in the development of colorectal tumors. For example, it has been reported that in patients with metabolic syndrome, glucagon-like peptide 1 plays an important role in glucose homeostasis by amplifying insulin secretion of oral nutrients[20] and actively participates in the development of colorectal adenomas.[21] Insulin resistance has been associated with the formation of colorectal tumors through many mechanisms and observational studies.[22,23] The gene *INSR*, which encodes an important component of the insulin pathway, may predict sensitivity to colorectal adenoma progression.[24]

Based on a previous study,[25] as well as the analysis of expression patterns of *INSR*, *KCNJ11*, and *PIK3CA* genes in adenomas, cancer and the normal control group from data found in the GEO database, an interesting phenomenon was found in that these three genes were different between the adenoma and control groups, but there was no statistical difference between CRC and the control group. In the process of tumor progression, colon adenocarcinoma usually progresses from adenoma to cancer, but some genes have interesting expression patterns. After the adenoma stage changes, certain genes gradually return to "normal" in the adenocarcinoma stage through adaptation and other mechanisms. These genes

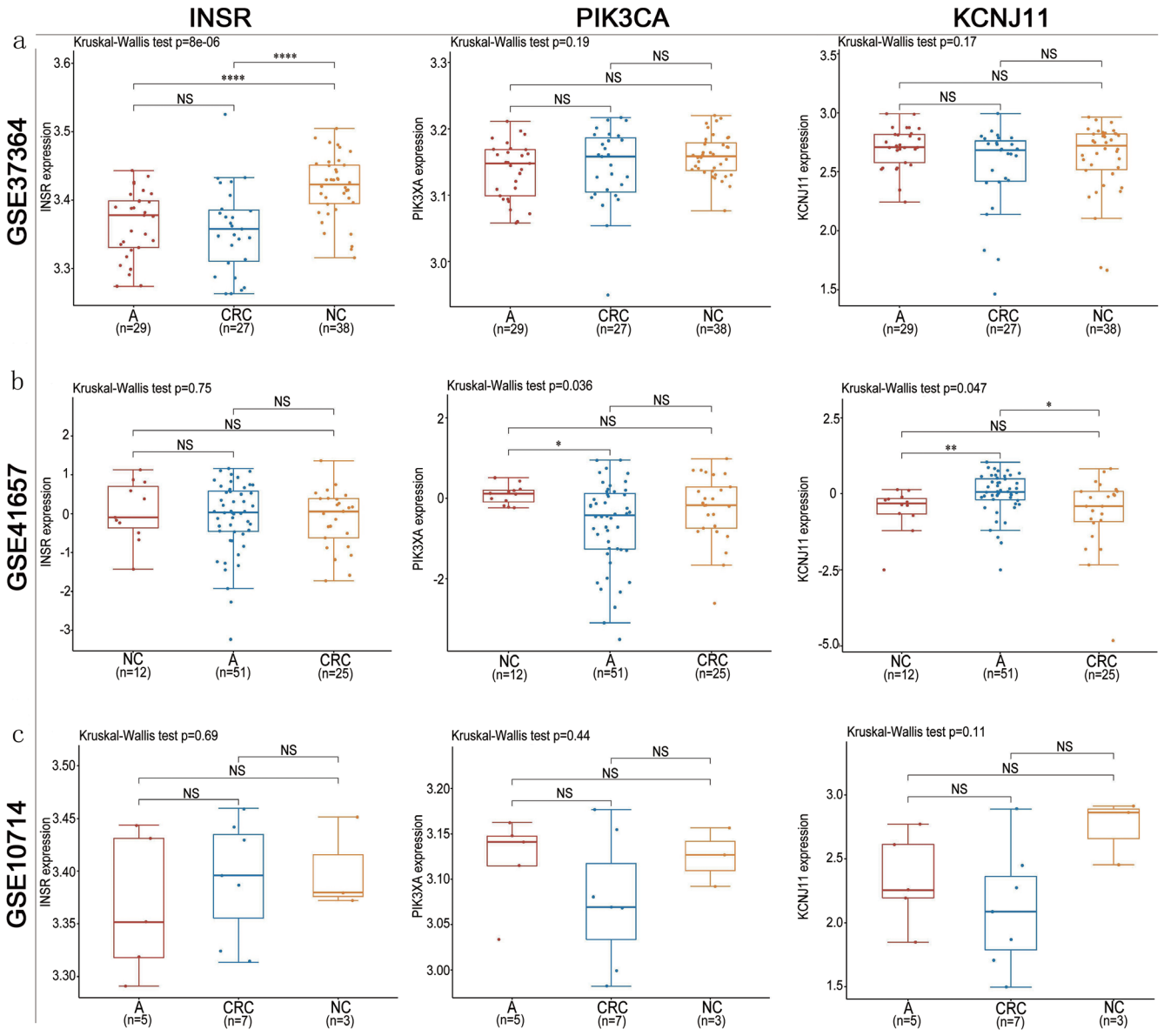

Fig. 4. *INSR*, *KCNJ11*, and *PIK3CA* gene expression from GEO database bioinformatics. INSR, insulin receptor; KCNJ11, potassium inwardly rectifying channel subfamily J member 11; PIK3CA, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha.

that only change in adenoma stage may be the key genes for early screening of CRC. As early as 1976, it was proposed that the development of tumor cells can be studied from the perspective of evolution.[26] Subsequent studies have also confirmed that the formation of a tumor follows the law of somatic evolution. Scientists from the United States and Germany have published a new study in the international academic journal Nature. Herein, entire exons of 538 patients with chronic lymphoblastic leukemia were sequenced with their corresponding embryonic DNA samples, and 44 genes were found to have repeated mutation, whereas 11 genes were found to have repeated copy number variations. These mutant genes include some novel genes (*RPS15, IKZF3ne*) that have not been reported previously but may drive cancer development. At the same time, they also found that RNA processing and transfer, myc activity and MAPK signaling are important pathways involved in chronic lymphocytic leukemia.[27] The transformation of energy metabolism is the basis for tumor cells to effectively adapt to changes in the microenvironment. *KCNJ11* is a protein coding gene, which can affect ATP-sensitive potassium channels (KATP channels), *KCNJ11*-related diseases, including hyperinsulinemia and hypoglycemia, play an important role in energy metabolism.[28]

Future directions

It was reported that *PIK3CA* may mutate in different pathological stages of CRC. The mutation could cause the decreased expression of *PIK3CA* in the adenoma stage, but increased expression during the adenocarcinoma stage. Therefore, it may be the reason that there is no statistical significant difference between healthy

control and CRC groups. Further research is necessary to increase samples, and divide the patients with colonic adenomas into two subgroups to detect the *PIK3CA* mutation, in order to explore important biomarkers in the progression of adenoma.

Conclusions

In summary, this study found that *INSR*, *KCNJ11*, and *PIK3CA* may act on colorectal adenomas through the insulin resistance pathway and promote the formation of progressive adenomas through clinical pathological data analysis, bioinformatics mining and molecular biology experiments. Therefore, the clinical monitoring of blood glucose and insulin levels can play a certain role in the occurrence and development of adenomas, and combined with the molecular levels of *INSR*, *KCNJ11*, and *PIK3CA*, are expected to play a role in the prevention and control of adenoma progression.

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Conflict of interest

The authors report no conflicts of interest in this work.

Author contributions

Study design, critical revision and critical funding administration (HZ); manuscript writing and performance of experiments (SJ); statistical analysis (LS, JH); analysis and interpretation of data (SW, LP, QY); technical support (JH, HP). All authors have made a significant contribution to this study and have approved the final manuscript.

Data sharing statement

No additional data are available.

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