空腹血糖与piR-30715的交互作用对胃癌术后患者预后的影响

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摘要 该文旨在探讨空腹血糖和PIWI蛋白相互作用RNA 30715(PIWI interacting RNA-30715, piR-30715)与胃癌预后的关系。于2014年9月~2016年10月, 收集福建省肿瘤医院收治的66例接受根治性胃切除术的胃癌患者。分析癌组织及癌旁组织的piR-30715、PIWI样蛋白4(PIWI-like 4, PIWIL4)表达情况; Kaplan-Meier生存曲线分析空腹血糖、piR-30715、PIWIL4与胃癌术后患者预后的关系; COX回归分析空腹血糖升高和piR-30715对胃癌术后患者预后的交互作用。与癌旁组织比, 癌组织的piR-30715、PIWIL4阳性表达例数明显增高(P<0.05)。随访截止到2020年12月31日, 66例胃癌随访时间为1.25~75.73个月, 中位随访时间为57.05个月。66例胃癌患者中, 25例(37.88%)死亡, 41例(62.12%)存活。单因素分析显示, 空腹血糖(OR=1.965, P<0.001)、piR-30715(OR=2.002, P=0.016)、PIWIL4阳性(OR=2.683, P=0.018)、分期(tumor node metastasis, TNM)(OR=5.755, P=0.018)、远处转移(OR=4.693, P=0.003)及淋巴结转移(OR=3.654, P=0.036)均与胃癌患者预后相关。COX分析显示, 空腹血糖升高和piR-30715高表达是胃癌预后的独立危险因素(P<0.05)。生存分析显示, 高空腹血糖组和piR-30715高表达组的胃癌患者的总体生存率较低(P<0.05)。空腹血糖和piR-30715对胃癌预后存在相乘交互作用($P_{相乘}$=0.003), 无相加交互作用(P>0.05)。空腹血糖升高和piR-30715高表达是胃癌预后的独立危险因素, 空腹血糖升高与piR-30715高表达对胃癌预后有相乘交互作用。

关键词 胃癌; 空腹血糖; piRNA-30715; PIWI样蛋白4; 预后; 交互作用

The Influence of the Interaction between Fasting Blood Glucose and piR-30715 on the Prognosis of Gastric Cancer Patients after Surgery

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Abstract The paper aimed to study the effect of fasting blood glucose levels and piR-30715 (PIWI interacting RNA 30715) expression on the prognosis of gastric cancer. A total of 66 patients with gastric cancer under-

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went radical gastrectomy were enrolled from September 2014 to October 2016. The expression of piR-30715 and PIWIL4 (PIWI-like 4) in cancer tissues and adjacent tissues was analyzed. The Kaplan-Meier survival curve was used to analyze the relationship between fasting blood glucose, piR-30715, PIWIL4 and postoperative prognosis of gastric cancer patients. The COX regression was used to study the interaction between fasting blood glucose, piR-30715 and the prognosis of postoperative gastric cancer patients. Compared with adjacent tissues, the expression of piR-30715 and PIWIL4 in cancer tissue was significantly increased (P<0.05). As of December 31, 2020, 66 cases of gastric cancer were followed up for 1.25 to 75.73 months, with a median follow-up time of 57.05 months. Among 66 gastric cancer patients, 25 (37.88%) died and 41 (62.12%) survived. The univariate analysis showed that fasting blood glucose (OR=1.965, P<0.001), piR-30715 (OR=2.002, P=0.016), PIWIL4 positive (OR=2.683, P=0.018), TNM (tumor node metastasis) staging (OR=5.755, P=0.018), distant metastasis (OR=4.693, P=0.003) and lymph node metastasis (OR=3.654, P=0.036) were all associated with the prognosis of gastric cancer patients. The COX analysis showed that elevated fasting blood glucose and higher expression of piR-30715 were independent risk factors for the prognosis of gastric cancer (P<0.05). The survival analysis showed that the overall survival rate of gastric cancer patients in the higer fasting blood glucose group and higher expression of piR-30715 group was lower (P<0.05). There is a multiplicative interaction between fasting blood glucose and piR-30715 on the prognosis of gastric cancer ($P_{multiplicative}$=0.003), but no additive interaction (P>0.05). Higher fasting blood glucose and higher expression of piR-30715 are independent risk factors for the prognosis of gastric cancer, and there is a multiplicative interaction between higher fasting blood glucose and higher expression of piR-30715 on the prognosis of gastric cancer.

Keywords gastric cancer; fasting blood glucose; piRNA-30715; PIWI like protein 4; prognosis; interaction

PIWI蛋白相互作用RNA(PIWI interacting RNA, piRNA)是一种新型的非编码小单链RNA(non-coding RNA), 其长度为26~31个核苷酸, 主要位于富含转座子序列的基因间区[1-2]。piRNAs在各类癌症中异常表达, piR-30715是piRNA的重要成员, 报道显示piR-30715在胃癌中异常表达, 与肿瘤浸润深度、分期及淋巴结转移等临床病理参数密切相关[3]。piRNAs可与PIWI蛋白家族成员特异性结合, 调节基因表达[3-4]。PIWI-piRNAs复合物通过抑制转座子的基因转录, 参与mRNA翻译调控和表观遗传调控, 从而维持基因组结构的稳定性[5-7]。PIWI样蛋白4(PIWI-like 4, PIWIL4)是已知的PIWI蛋白家族中的4种亚型之一, 在人体组织广泛表达, 主要通过介导组蛋白H3赖氨酸9(histone H3 at lysine 9, H3K9)甲基化参与修饰细胞染色质[8-9]。越来越多的证据表明, PIWI-piRNA复合物在恶性肿瘤组织中明显异常表达[10-11]。

胃癌(gastric cancer, GC)是最常见的恶性肿瘤, 居恶性肿瘤死亡率第2位[12]。由于早期临床症状隐匿, 一旦确诊, 胃癌患者多为中晚期, 可用的治疗方法常常不能令人满意。除此之外, 最近的研究表明, 高血糖与慢性全身性炎症以及胃癌的发病率和死亡风险增加有关[13-14]。动脉粥样硬化和肿瘤存在一些共同的病理生理基础, 如慢性炎症、细胞增殖迁移和氧化应激等。研究显示, 高血糖是胃癌、食道癌和结直肠癌等多种癌症的不良预后因素[15-17]。因此, 探索有效的胃癌早期诊断指标, 加强早期血糖筛查, 可有效改善胃癌预后, 延长患者生存期。

本研究评估空腹血糖和piR-30715、PIWIL4表达之间的相关性, 探究空腹血糖和piR-30715对胃癌术后预后的影响是否存在交互作用以及交互作用的强度如何, 旨在为寻找一种新的预测胃癌预后的生物标志物。

1 材料和方法

1.1 研究人群

选取2014年9月~2016年10月在福建省肿瘤医院住院的胃癌根治术后的患者。本研究共纳入66例患者。本研究经福建省肿瘤医院伦理委员会批准(批准号: SQ2015-070-01), 并获得所有患者的知情同意。

1.2 纳入/排除标准

纳入标准: (1) 胃癌患者均为首次确诊, 术前均未接受过任何治疗; (2) 均接受胃癌根治术, 术后经病理学证实为胃癌; (3) 未出现全身广泛性转移或衰

表1 基因及序列

Table 1 Genes and sequences

基因 Genes	序列 Sequences
PIWIL4	Upstream: 5′-CAT GAA CTA CTG GCA TCA C-3′
	Downstream: 5′-GGG AAT TAG ACT CTG TTA TC-3′
β-actin	Upstream: 5′-CGT GAC ATT AAG GAG AAG CTG-3′
	Downstream: 5′-CTA GAA GCA TTT GCG GTG GAC-3′

竭症状; (4) 签署知情同意书。排除标准: (1) 合并其他原发肿瘤; (2) 合并心脏受损、脑血管疾病、严重肝肾功能不全或感染性疾病者; (3) 脏器及淋巴结转移者。

1.3 实时RT-PCR检测及亚组分组

新鲜组织经外科手术切除后立即储存入液氮, 采集和保存操作均按照无酶原则进行。采用RNA提取试剂盒(德国QIAGEN公司)提取66例胃癌及癌旁组织总RNA。根据制造商的说明, 采用miScript逆转录试剂盒(广州锐博生物技术有限公司)进行逆转录, 委托广州锐博合成piRNA和*PIWIL4*的引物。以内参5S rRNA和*β-actin*(广州锐博物技术有限公司)对各基因表达进行标准化, 使用$2^{-\Delta\Delta Ct}$方法计算相对表达量(relative quantification, RQ), RQ值取常用对数lg进行分析。将癌组织的piR-30715表达水平>对应癌旁组织的患者纳入高表达组, 将癌组织的piR-30715表达水平≤对应癌旁组织的患者纳入低表达; 将PIWIL4表达水平>0.653纳入阳性表达, 将癌组织的PIWIL4表达水平≤0.653纳入阴性表达[18]。基因及序列见表1。

1.4 出院随访

患者出院后均接受随访, 随访包括门诊复查和电话随访相结合的方式。随访时间从确诊至末次随访或死亡, 如果发生胃癌死亡, 确切日期由亲属或医疗报告记录。临床终点事件为胃癌死亡。

1.5 患者临床特征

禁食8~12 h, 于次日清晨抽取肘静脉血。记录年龄、性别、体质量指数(body mass index, BMI)、总胆固醇、三酰甘油、低密度脂蛋白胆固醇(low density lipoprotein cholesterol, LDL-C)、高密度脂蛋白胆固醇(high density lipoprotein cholesterol, HDL-C)、载脂蛋白A(apolipoprotein-A, APO-A)、载脂蛋白B(apolipoprotein-B, APO-B)和空腹血糖。年龄以首次入院时的年龄为标准。

1.6 统计分析

采用SPSS 22.0统计软件分析。正态分布的计量资料用均数±标准差($\bar{x}\pm s$)表示, 两组间比较采用t检验; 不符合正态分布时用中位数(四分位数间距), 两组间比较采用秩和检验。计数资料用百分数表示, 两组间比较采用卡方检验。COX分析影响胃癌预后的危险因素。采用生存曲线分析空腹血糖和piR-30715表达与生存的关系。空腹血糖和piR-30715的交互作用采用相乘交互模型和相加交互模型[19-20]。COX回归模型分析空腹血糖和piR-30715的相乘交互作用。Andersson编制的Excel计算表评价两组间的相加交互作用[21], 记录超额相对危险(relative excess risk due to interaction, RERI)、交互作用归因比(attributable proportion due to interaction, AP)、交互作用指数(synergy index, S)和95%置信区间(confidence interval, CI)等参数。以P<0.05为差异有统计学意义。

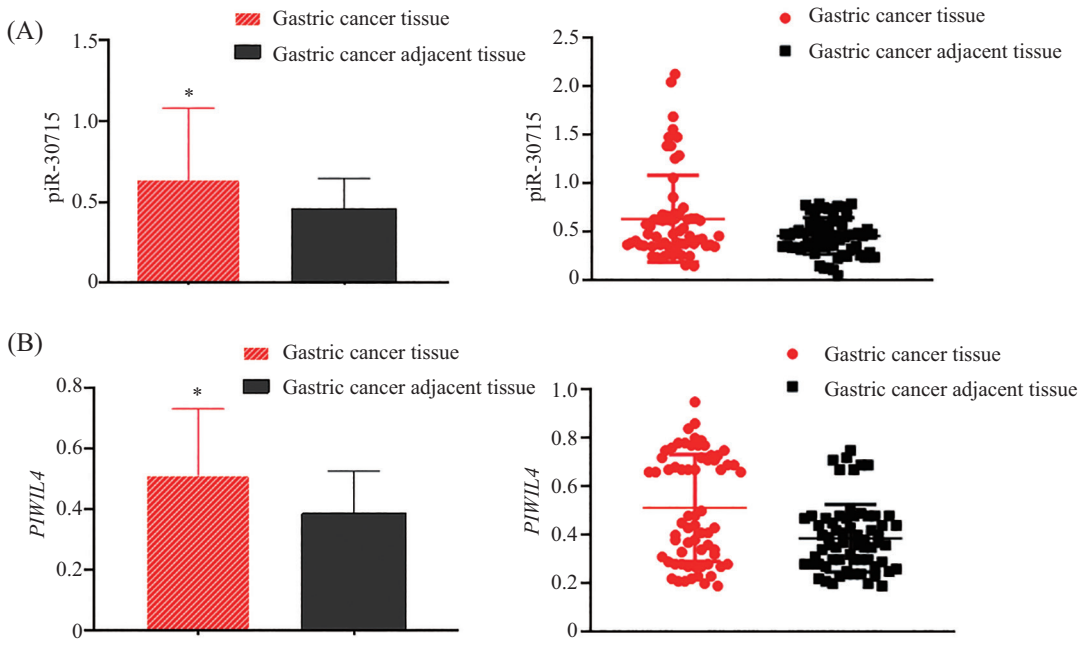
2 结果

2.1 癌组织及癌旁组织的piR-30715、*PIWIL4*表达比较

66例胃癌患者癌组织及癌旁组织的piR-30715表达水平分别为(0.64±0.45)、(0.46±0.19), PIWIL4阳性表达患者分别为30例(45.45%)和7例(10.61%), 表达水平分别为(0.51±0.22)、(0.39±0.14), 与癌旁组织相比, 癌组织的piR-30715、PIWIL4表达水平明显增高(t=2.994, 3.739, P<0.05)(图1)。

2.2 死亡和存活组患者的临床基线特征

随访截止时间为2020年12月31日, 随访时间为1.25~75.73个月, 中位随访时间为57.05个月。66例胃癌患者中, 25例(37.88%)死亡, 41例(62.12%)存活。两组患者的年龄、性别、BMI、吸烟情况、APOA、APOB、收缩压(systolic blood pressure, SBP)、舒张压(diastolic blood pressure, DBP)、总



A: 癌组织及癌旁组织的piR-30715表达柱状图及散点图; B: 癌组织及癌旁组织的PIWIL4表达柱状图及散点图。*P<0.05, 与癌旁组织比。

A: histogram and scatter plot of piR-30715 expression in cancer tissues and adjacent tissues; B: histogram and scatter plot of PIWIL4 expression in cancer tissues and adjacent tissues. *P<0.05 compared with gastric cancer adjacent tissues.

图1　癌组织及癌旁组织的piR-30715、*PIWIL4*表达

Fig.1　Expression of piR-30715 and *PIWIL4* in gastric cancer tissues and adjacent tissues

胆固醇(total cholesterol, TC)、高密度脂蛋白(high density lipoprotein cholesterol, HDL)、低密度脂蛋白胆固醇(low density lipoprotein cholesterol, HDL)、甘油三酯(triacylglycerol, TG)等差异无统计学意义(P>0.05)。与死亡组相比, 存活组的空腹血糖、piR-30715、PIWIL4表达水平较高、分期(tumor node metastasis, TNM)较高、肿瘤浸润深度、淋巴结转移(lymph node metastasis, LNM)和远处转移的例数较多(P<0.05)(表2)。

2.3　piR-30715与胃癌临床病理特征的关系

TNM III+IV期胃癌组piR-30715的相对表达量明显高于I+II期(P<0.001); 肿瘤浸润深度T2+T3+T4 piR-30715的相对表达量明显高于T1组(P<0.001); 淋巴结转移piR-30715相对表达量明显高于无淋巴结转移(P<0.001)。piR-30715的表达与性别、年龄、肿瘤大小、Lauren's分型及远处转移均无统计学差异(P>0.05)(表3)。

2.4　胃癌预后因素的COX回归分析

采用COX风险比例模型对66例胃癌术后潜在预后因素做COX回归, 单因素COX分析显示空腹血糖、piR-30715、PIWIL4阳性、TNM分期、远处转移及淋巴结转移与胃癌术后预后相关(P<0.05)。将上述因素纳入多因素COX风险比例模型, 结果显示空腹血糖升高和piR-30715高表达是胃癌术后预后的独立危险因素(P<0.05)(表4)。

2.5　空腹血糖与胃癌根治术后患者的Kaplan-Meier生存分析

根据空腹血糖中位数将胃癌患者分为两组。空腹血糖<5.84 mmol/L的患者生存时间明显延长。高空腹血糖组20例, 死亡15例, 生存时间(30.50±5.98)个月; 低空腹血糖组46例, 死亡10例, 生存时间(68.56±2.34)个月。Kaplan-Meier分析法绘制生存曲线图, 高空腹血糖组的胃癌患者的总体生存率较低(P<0.001)(图2)。

2.6　piR-30715与胃癌根治术后患者的Kaplan-Meier生存分析

piR-30715高表达组17例, 死亡10例, 平均生存时间(46.26±6.22)个月; piR-30715低表达组49例, 死亡15例, 平均生存时间(60.55±3.70)个月。采用Kaplan-Meier生存分析绘制生存曲线图, piR-30715高表达组的胃癌患者的总体生存率较低(P=0.032)(图3)。

2.7　空腹血糖与piR-30715表达的相乘及相加交互作用对胃癌预后的影响

对空腹血糖与piR-30715对胃癌预后的影响进

表2 死亡和存活组患者的临床基线特征

Table 2 Clinical baseline characteristics of deaths and survivors

特征 Features	死亡组(n=25) Dead group (n=25)	存活组(n=41) Survival group (n=41)	t/χ^2/Z value	P value
Age /years	59.83±10.16	61.25±8.32	0.618	0.540
Males /%	10 (40.00%)	25 (60.98%)	2.743	0.098
BMI /kg·m^{-2}	22.11±3.08	23.17±2.35	1.578	0.122
Smoking /%	6 (24.00%)	8 (19.51%)	0.187	0.665
SBP /mmHg	120.00 (111.50, 135.00)	120.00 (115.00, 131.25)	0.588	0.879
DBP /mmHg	78.00 (70.00, 80.00)	75.00 (70.00, 80.00)	0.726	0.668
FBG /mmol·L^{-1}	6.69 (5.38, 8.40)	4.84 (4.49, 5.45)	2.059	0.000
TG /mmol·L^{-1}	0.78 (0.63,1.06)	1.07 (0.84, 1.45)	1.216	0.104
TC /mmol·L^{-1}	4.62 (4.02, 5.25)	4.58 (4.00, 5.10)	0.333	0.999
HDL /mmol·L^{-1}	1.54 (1.21, 1.79)	1.32 (1.09, 1.56)	1.255	0.086
LDL /mmol·L^{-1}	3.20±1.04	3.09±0.87	0.462	0.646
APO-A /mmol·L^{-1}	1.40 (1.20, 1.50)	1.30 (1.10, 1.48)	0.922	0.363
APO-B /mmol·L^{-1}	0.95 (0.80, 1.08)	1.00 (0.80, 1.10)	0.530	0.942
piR-30715 expression	0.92±0.69	0.46±0.74	2.512	0.016
PIWIL4 (+)	16 (64.00%)	14 (34.15%)	5.583	0.018
TNM staging			6.636	0.010
I-II	2 (8.00%)	15 (36.59%)		
III-IV	23 (92.00%)	26 (63.41%)		
Depth of tumor invasion			3.893	0.048
<T2	1 (4.00%)	9 (21.95%)		
⩾T2	24 (96.00%)	32 (78.05%)		
Distant metastasis	5 (20.00%)	1 (2.44%)	---*	0.001
LNM	22 (80.00%)	25 (60.98%)	5.533	0.019
Lauren's classification			3.294	0.070
Intestinal type	6 (24.00%)	19 (46.34%)		
Diffuse type	19 (76.00%)	22 (53.66%)		
Maximum tumor diameter >5cm	17 (68.00%)	18 (43.90%)	3.621	0.057

BMI=体质量指数; SBP=收缩压; DBP=舒张压; FBG=空腹血糖; TG=三酰甘油; TC=总胆固醇; HDL=高密度脂蛋白胆固醇; LDL=低密度脂蛋白胆固醇; TNM=分期; LNM=淋巴结转移; APO-A=载脂蛋白A、APO-B=载脂蛋白B; PIWIL4=PIWI样蛋白4; ---*: Fisher精确检验, 无c^2值。

BMI=body mass index; SBP=systolic blood pressure; DBP=diastolic blood pressure; FBG=fasting blood glucose; TG=triacylglycerol; TC=total cholesterol; HDL=high density lipoprotein cholesterol; LDL=low density lipoprotein cholesterol; TNM=tumor node metastasis; LNM=lymph node metastasis; APO-A=apolipoprotein-A, APO-B=apolipoprotein-B; PIWIL4=PIWI-like 4; ---*: Fisher's exact test, no c^2 value.

行了交互作用分析, 纳入空腹血糖与piR-30715表达的乘积项, 调整性别、年龄、BMI、吸烟情况、血压、TG、CHOL、HDLC、LDLC、APO-A、APO-B后, COX回归模型分析空腹血糖与piR-30715表达对胃癌预后存在相乘交互作用($P_{相乘}$=0.003)(表5)。

相加交互作用分析显示, 空腹血糖与piR-30715表达的95%置信区间(CI)之间的RERI、AP和S分别为2.030(–3.503~7.563)、0.406(–0.356~1.169)和2.032(0.317~13.030), RERI和AP的置信区间包括0, S包括1, 无统计学相加交互作用(表6)。

3 讨论

本研究结果显示, 与66例癌旁组织比, 66例癌组织的piR-30715、PIWIL4表达水平明显增高, 且piR-30715表达与TNM分期、肿瘤浸润深度和淋巴结转移密切相关(表3), 提示piR-30715、PIWIL4可能参与了胃癌的发生发展过程。*PIWIL4*基因的瞬时转染诱导H3K9在p16Ink4a位点甲基化, 导致*p16Ink4a*基因下调, 继而修饰人类细胞染色质[22]。我们假设piR-30715可与PIWIL4结合形成PIWI-piRNAs复合物, 通过组蛋白H3K9的甲基化或在细胞核周围形成异染色质来促进细胞增殖、迁移和侵袭。多项研究表

表3 piR-30715与胃癌临床病理特征的关系

Table 3 Relationship between piR-30715 and clinicopathological features of gastric cancer

临床病理特征 Clinicopathological features	例数 Cases	piR-30715		
		lgRQ	*t* value	*P* value
Gender			0.971	0.335
Male	50	0.61±0.41		
Female	16	0.73±0.55		
Age /years			0.315	0.754
<60	38	0.62±0.44		
≥60	28	0.66±0.47		
Lauren's classification			1.197	0.236
Intestinal type	25	0.55±0.43		
Diffuse type	41	0.69±0.45		
Tumor diameter /cm			0.920	0.361
<5	30	0.58±0.37		
≥5	36	0.68±0.50		
TNM stage			7.127	0.000
I-II	18	0.28±0.07		
III-IV	48	0.77±0.46		
Depth of tumor invasion			7.752	0.000
<T2	11	0.24±0.04		
≥T2	55	0.72±0.45		
Distant metastasis			1.250	0.216
No	60	0.62±0.42		
Yes	6	0.85±0.67		
LNM			7.105	0.000
No	19	0.29±0.07		
Yes	47	0.78±0.46		

TNM=分期; LNM=淋巴结转移。

TNM=tumor node metastasis; LNM=lymph node metastasis.

表4 胃癌预后因素的COX回归分析

Table 4 COX regression analysis of prognostic factors of gastric cancer

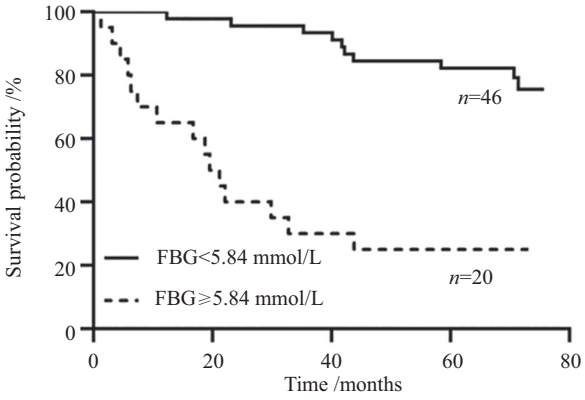
参数 Parameters	单因素分析 Single factor analysis			多因素分析 Multivariate analysis		
	OR	95% CI	*P* value	OR	95% CI	*P* value
FBG	1.965	1.581-2.443	0.000	2.014	1.512-2.683	<0.000
piR-30715	2.002	1.140-3.513	0.016	2.418	1.084-5.393	0.031
PIWIL4 (+)	2.683	1.181-6.096	0.018			
TNM staging	5.755	1.352-24.504	0.018			
Distant metastasis	4.693	1.711-12.874	0.003			
LNM	3.654	1.090-12.255	0.036			

FBG=空腹血糖; TNM=分期; LNM=淋巴结转移。TNM staging、Distant metastasis及LNM多因素分析均*P*>0.05。

FBG=fasting blood glucose; TNM=tumor node metastasis; LNM=lymph node metastasis. There were no significant differences in TNM staging, Distant metastasis and LNM with multivariate analysis (*P*>0.05).

明, piRNA能够穿过细胞膜并进入循环系统, 抵抗人体血液中存在的核糖核酸酶的降解[23-24], 因而piR-30715有望成为胃癌预后的潜在生物标志物。

随访时间1.25~75.73个月, 66例胃癌患者中, 25例(37.88%)死亡, 41例(62.12%)存活。经单因素、COX分析显示, 空腹血糖升高和piR-30715高表达均是胃

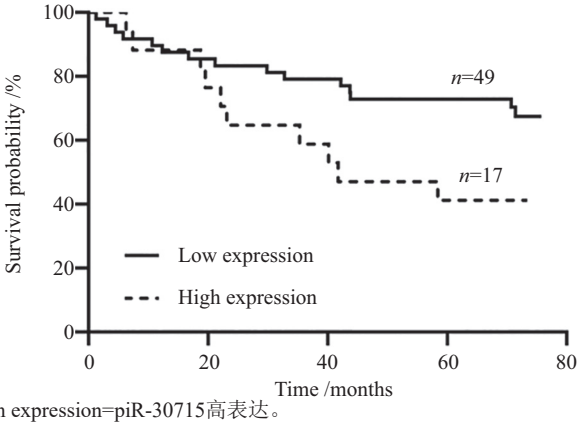


FBG=空腹血糖。

FBG=fasting blood glucose.

图2 空腹血糖与胃癌术后的Kaplan-Meier生存分析

Fig.2 Kaplan-Meier survival analysis of FBG and prognosis of gastric cancer



Low expression=piR-30715低表达; high expression=piR-30715高表达。

Low expression=low expression of piR-30715; high expression=high expression of piR-30715.

图3 piR-30715与胃癌术后的Kaplan-Meier生存分析

Fig.3 Kaplan-Meier survival analysis of expression of piR-30715 and prognosis of gastric cancer

表5 空腹血糖与piR-30715表达的相乘交互作用对胃癌预后的影响

Table 5 Effect of multiplication interaction between FBG and piR-30715 expression on prognosis of gastric cancer

参数 Parameter	β	OR	95% CI	*P* value
piR-30715	1.009	2.744	1.160-6.491	0.022
FBG	0.877	2.404	1.726-3.348	<0.001
piR-30715 FBG	0.213	1.237	1.075-1.424	0.003

FBG=空腹血糖; β: 回归系数β; OR=比值比; 95% CI=95%置信区间; FBG=空腹血糖。

FBG=fasting blood glucose; β=regression coefficient β; OR=odds ratio; 95% CI=95% confidence interval; FBG= fasting blood glucose.

表6 空腹血糖与piR-30715表达的相加交互作用

Table 6 Additive interaction between FBG and piR-30715

参数 Parameters	超额相对危险 RERI		交互作用归因比 AP		交互作用指数 S	
	Point estimate	95% CI	Point estimate	95% CI	Point estimate	95% CI
piR-30715 & FBG	2.030	–3.503-7.563	0.406	–0.356-1.169	2.032	0.317-13.030

FBG=空腹血糖; RERE=超额相对危险; AP=交互作用归因比; S=交互作用指数。

FBG=fasting blood glucose; RERE=excess relative risk; AP=attributable proportion due to interaction; S=interaction index.

癌术后预后的独立危险因素(表4), 生存分析显示, 空腹血糖升高和piR-30715高表达患者的总体生存率均较低(图2和图3), 该结果与文献报道类似[25-26]。空腹血糖与胃癌预后密切相关可能原因有以下几点: (1) 空腹血糖较高已被广泛研究为胃癌的预后危险因素[27-29], 葡萄糖是癌细胞增殖的基础, 为肿瘤生长提供了适宜的条件, 高血糖可能通过产生氧自由基和酸直接导致DNA损伤[30], 间接辅助胃癌发生发展; (2) 空腹血糖较高与胰岛素抵抗、促炎状态和氧化应激有关, 有助于直接促进胃癌发生, 其中胰岛素抵抗和随之而来的高胰岛素血症可能导致胰岛素样生长因子(insulin like growth factor, IGF)水平升高, IGFs受体的过表达和IGF结合蛋白(insulin-like growth factor binding proteins, IGFBPs)的异质表达在胃癌的发生、发展和转移中发挥重要作用。piR-30715与胃癌预后密切相关可能原因有以下几点: (1) 成年大鼠胰岛中*PIWIL2*或*PIWIL4*基因的沉默导致多种piRNA水平降低, 继而导致胰岛素分泌缺陷和细胞对细胞因子诱导的细胞死亡的抵抗力增加, 在糖尿病大鼠中上调piRNA, 胰岛的piRNA过度表达, 导致葡萄糖诱导的胰岛素释放呈选择性缺陷, 血糖水平显著增高; (2) piR-30715基因及蛋白可能参与调控β细胞功能, 上调血糖[31], 如前所述, 血糖升高可直接或间接诱导胃癌发生发展。经以上分析不难得到, 空腹血糖与piR-30715表达对胃癌术后预后具有协同作用, 如本研究在校正性别、年龄、BMI、吸烟情况、血压、TG、CHOL、HDLC、LDLC、APO-A和APO-B混杂因素后, 空腹血糖与piR-30715表达对胃癌预后存在相乘交互作用($P_{相乘}$=0.003)(表4), 该结果提示了空腹血糖与piR-30715可协同发挥促癌作用, 因此, 当临床发现空腹血糖升高或piR-30715高表达水平患者时, 医生需要警惕, 尤其是当这两种危险因素同时存在时, 患者应接受更多癌变排查的检查, 尤其应接受检查胃癌敏感性指标。空腹血糖和piR-30715表达如何协同参与胃癌发生发展的机制仍需要进一步探索。但PIWIL4表达与胃癌术后预后无明显的关联, 该结果是否与PIWIL4通过复合物方式参与胃癌发生过程而非游离蛋白表达相关, 仍需要进一步分析。

本研究存在一些局限性: (1) 本研究的样本量偏小且来源于单中心研究, 可能对结果的分析有一定的影响; (2) 本研究中的数据仅采用单次测量的数据进行分析, 随访中空腹血糖的改变可能会对结果造成影响。虽然大多数混杂因素得到控制, 但由于我们研究的上述局限性, 未考虑一些潜在的混杂因素, 例如抗糖尿病药物的使用, 因此未来仍需要进一步研究验证空腹血糖升高和piR-30715高表达对胃癌术后预后的预测价值, 并探索其相关的信号通路。最后, 考虑到只分析了胃癌术后患者, 我们的研究结果不应直接外推到所有胃癌患者。

综上所述, 空腹血糖升高和piR-30715高表达均是胃癌预后的独立危险因素, 空腹血糖与piR-30715表达对胃癌预后存在相乘交互作用。

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