

胆管癌患者血清 circRNA MBOAT2, circRNA ACTN4 水平表达与临床病理特征及预后的关系研究

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摘要:目的 探究胆管癌患者血清环状RNA膜结合O-酰基转移酶2(circRNA MBOAT2)和环状RNA辅肌动蛋白 α 4(circRNA ACTN4)的表达变化及其与预后的关系。方法 选择2021年1月~2024年1月在邯郸市第一医院诊治的96例胆管癌患者作为胆管癌组,另选85例胆管内结石患者和90例健康志愿者分别作为结石组和对照组。定量实时反转录聚合酶链式反应(qRT-PCR)检测血清circRNA MBOAT2, circRNA ACTN4水平,分析circRNA MBOAT2, circRNA ACTN4与临床病理特征的关系; Pearson分析胆管癌患者circRNA MBOAT2, circRNA ACTN4的相关性; ROC分析circRNA MBOAT2, circRNA ACTN4对胆管癌发生的诊断价值; COX分析胆管癌患者预后不良的影响因素; Kaplan-Meier生存曲线法进行生存分析。结果 胆管癌组血清circRNA MBOAT2(1.24 ± 0.38), circRNA ACTN4(1.27 ± 0.42)高于结石组(1.02 ± 0.31 , 1.05 ± 0.34)和对照组(0.83 ± 0.24 , 0.78 ± 0.21), 结石组高于对照组, 差异具有统计学意义($t=5.016 \sim 14.025$, 均 $P<0.05$)。胆管癌组患者circRNA MBOAT2与circRNA ACTN4呈正相关($r=0.428$, $P<0.05$); circRNA MBOAT2, circRNA ACTN4联合诊断胆管癌发生优于单独诊断($Z=4.063$, 4.004 , 均 $P<0.05$); circRNA MBOAT2, circRNA ACTN4与临床分期、淋巴结状态相关($t=5.091 \sim 5.984$, 均 $P<0.05$); 淋巴结状态阳性、circRNA MBOAT2, circRNA ACTN4升高为患者死亡的独立危险因素($HR=1.527$, 1.582 , 1.727 , 均 $P<0.05$)。高表达circRNA MBOAT2(23.40%), circRNA ACTN4(24.00%)的患者累积生存率均低于低表达(46.94%, 47.83%)患者, 差异具有统计学意义($\chi^2=5.809$, 5.946 , 均 $P<0.05$)。结论 circRNA MBOAT2, circRNA ACTN4水平随着疾病进展升高, 联合检测对诊断胆管癌发生具有一定价值, 是患者死亡的独立危险因素。

关键词:胆管癌; 环状RNA膜结合O-酰基转移酶2; 环状RNA辅肌动蛋白 α 4; 诊断价值; 病理特征

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Study on the Relationship between the Expression of Serum circRNA MBOAT2 and circRNA ACTN4 Levels and Clinicopathological Features and Prognosis in Patients with Cholangiocarcinoma

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Abstract: Objective To investigate the expression changes of serum circRNA membrane bound O-acyltransferase 2 (circRNA MBOAT2) and circRNA recombinant actinin 4 (circRNA ACTN4) in patients with cholangiocarcinoma and their relationship with prognosis. **Methods** 96 patients with cholangiocarcinoma treated at the First Hospital of Handan City from January 2020 to January 2022 in Department of Hepatobiliary Surgery were regarded as the cholangiocarcinoma group. Additionally, 85 patients with intraductal stones and 90 healthy volunteers were collected as the stone group and control group, respectively. Quantitative real-time reverse transcription PCR(qRT-PCR) was applied to detect the expression levels of circRNA MBOAT2 and circRNA ACTN4. χ^2 test was applied to analyze the relationship between circRNA MBOAT2 and circRNA ACTN4 and clinical pathological features. Pearson was applied to analyze the correlation between circRNA MBOAT2 and circRNA ACTN4 in patients with cholangiocarcinoma. ROC was applied to analyze the diagnostic value of circRNA MBOAT2 and circRNA ACTN4 in the occurrence of cholangiocarcinoma. COX was applied to analyze the influencing factors of poor prognosis in patients with cholangiocarcinoma. Kaplan-Meier method was applied for survival analysis. **Results** circRNA MBOAT2(1.24 ± 0.38) and circRNA ACTN4(1.27 ± 0.42) in cholangiocarcinoma group were higher than those in stone group(1.02 ± 0.31 , 1.05 ± 0.34) and control group(0.83 ± 0.24 , 0.78 ± 0.21), and the stone group was higher than that in control group, with statistically significance

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($t=5.016 \sim 14.025$, all $P<0.05$). There was a positive correlation between circRNA MBOAT2 and circRNA ACTN4 in patients with cholangiocarcinoma group ($r=0.428$, $P<0.05$). Combined diagnosis of MBOAT2 and ACTN4 was better than single diagnosis of cholangiocarcinoma ($Z=4.063$, 4.004 , all $P<0.05$); circRNA MBOAT2 and circRNA ACTN4 were correlated with clinical staging and lymph node status ($t=5.091 \sim 5.984$, all $P<0.05$). Positive lymph node status and elevated levels of circRNA MBOAT2 and circRNA ACTN4 were independent risk factors for mortality (HR=1.527, 1.582, 1.727, all $P<0.05$). The cumulative survival rate of patients with high expression of circRNA MBOAT2(23.40% vs 46.94%) and circRNA ACTN4(24.00% vs 47.83%) was lower than that of patients with low expression ($\chi^2=5.809$, 5.946, all $P<0.05$). **Conclusion** The serum levels of circRNA MBOAT2 and circRNA ACTN4 increase with the progression of the disease, and the combination of the two has certain value in diagnosing the occurrence of cholangiocarcinoma.

Keywords: cholangiocarcinoma; circular RNA membrane-bound O-acyltransferases 2; circRNA actinin 4; diagnostic value; pathological features

胆管癌(cholangiocarcinoma)是一种高度致命的上皮细胞恶性肿瘤,由胆道内不同部位引起的一系列具有侵袭性的恶性肿瘤,是仅次于肝细胞癌(hepatocellular carcinoma, HCC)的第二大原发性肝脏恶性肿瘤^[1]。胆管癌是一种罕见的癌症,由于慢性胆道炎症(胆结石、原发性硬化性胆管炎等)的致癌作用,其发病率和死亡率不断上升。目前手术切除是唯一有可能治愈的方法,但大部分患者并不具有局部切除的条件,生存时间将大打折扣^[2]。因此,预防和个性化治疗是目前延长患者生存时间的重要途径。环状RNA(circular RNA, circRNA)是一种不具有蛋白质编码能力的新型RNA,具有稳定、保守和表达特异性的特点。研究人员发现, circRNA通过吸收能够在转录后水平发挥作用的微小RNA在细胞质中高度表达^[3]。circRNA的疾病特异性表达使其可用作癌症治疗的分子标记,如膜结合O-酰基转移酶2(membrane-bound O-acyltransferases, MBOAT2)在胰腺癌组织和细胞中表达明显升高,沉默其表达能够在体内抑制肿瘤形成^[4]。辅肌动蛋白 α 4(recombinant alpha actinin 4, ACTN4)是一种来自辅肌动蛋白4的新的环状RNA,在调节乳腺癌细胞的耐药性和细胞恶性行为中发挥重要作用^[5]。circRNA MBOAT2, circRNA ACTN4在癌症中具有重要作用,但在胆管癌中少有报道,因此,本研究拟探究circRNA MBOAT2, circRNA ACTN4在胆管癌患者中表达变化及与患者预后的关系。

1 材料与方法

表 1

qRT-PCR 引物序列

基因	上游引物	下游引物
circRNA MBOAT2	5'-ATGCCTTACACTTCTTG-3'	5'-GAGCTAGTTTTGCTTGAA-3'
circRNA ACTN4	5'-AGCAGGTCTCTACCCCATC-3'	5'-TAATC GGGGAGCACTTGAGC-3'
GAPDH	5'-AGAAGGCTGGGGCTCATTG-3'	5'-AGGGGCCATCCACAGTCTTC-3'

1.3.2 随访:对胆管癌患者进行为期两年的门诊复查,每三个月一次,最后随访时间为患者死亡或最后一位患者随访结束,无失访病例。其中34例患者生存,62例患者死亡。

1.1 研究对象 本研究选择2021年1月~2024年1月在邯郸市第一医院诊治的96例胆管癌患者作为胆管癌组,其中男性51例,女性45例,年龄 48.63 ± 11.28 岁。另选取85例胆管内结石患者和90例健康志愿者作为结石组和对照组,其中结石组男性47例,女性38例,年龄 47.32 ± 10.67 岁;对照组男性42例,女性48例,年龄 48.64 ± 11.34 岁;三组一般资料比较差异无统计学意义($\chi^2/F=1.431$, 0.418 , all $P<0.05$)。纳入标准:①病理学确诊为胆管癌;②结石组经影像学确诊;③临床资料完整;④受试者本人和家属同意参与本研究。排除标准:①合并其他肿瘤;②胆发育畸形;③心脑血管疾病;④入组前接受过放疗;⑤不能配合完成检测及后期随访者。本研究经医院伦理委员会审核批准(20240201)。

1.2 仪器与试剂 低温离心机(赛默飞), RNA提取、反转录、qRT-PCR试剂盒(诺唯赞), 引物在生工生物工程(上海)股份有限公司合成。

1.3 方法

1.3.1 引物序列:取受试者治疗前(对照组取体检当天)空腹状态下静脉血5ml,低温离心后取上清,提取RNA后反转录为cDNA, Primer Premier 5软件进行引物设计后送去生工生物公司合成引物,引物序列见表1。定量实时反转录聚合酶链式反应(quantitative real-time reverse transcription PCR, qRT-PCR)技术以GAPDH为内参, $2^{-\Delta\Delta Ct}$ 方法计算circRNA MBOAT2, circRNA ACTN4表达量。反应程序:94℃ 5min, 94℃ 30s, 58℃ 30s, 72℃ 30s, 32个循环。

1.4 统计学分析 采用SPSS 25.0软件进行数据分析。计量资料以均数 \pm 标准差($\bar{x}\pm s$)表示,两组之间比较采用 t 检验;计数资料以 $n(\%)$ 表示,两组之间比较采用 χ^2 检验;并分析circRNA MBOAT2, circRNA

ACTN4表达与患者临床病理特征的关系。Pearson分析circRNA MBOAT2, circRNA ACTN4的相关性。受试者工作特征(ROC)曲线分析circRNA MBOAT2, circRNA ACTN4对胆管癌发生的诊断价值, Z检验比较曲线下面积(AUC)的差异。COX分析胆管癌患者预后不良的影响因素; Kaplan-Meier生存曲线法进行生存分析, 组间生存曲线差异用对数秩检验(Log-Rank test)。P<0.05为差异具有统计学意义。

2 结果

2.1 三组circRNA MBOAT2, circRNA ACTN4水平比较及两者相关性分析 对照组、结石组、胆管癌组 血清circRNA MBOAT2(0.85±0.24, 1.02±0.31, 1.24±0.38), circRNA ACTN4(0.78±0.21, 1.05±0.34, 1.27±0.42)表达依次升高, 差异具有统计学意义(F=35.458, 49.247, 均P<0.05)。血清circRNA MBOAT2, circRNA ACTN4胆管癌组表达高于结石组和对照组(t=6.592, 11.861; 6.203, 14.025), 结石组高于对照组(t=5.016, 7.497), 差异具有统计学意义(均P<0.05)。Pearson分析结果显示: circRNA MBOAT2与circRNA

ACTN4呈正相关(r=0.428, P=0.000)。

2.2 circRNA MBOAT2, circRNA ACTN4对胆管癌发生的诊断价值 见表2, 图1。circRNA MBOAT2, circRNA ACTN4联合诊断优于单独诊断, 差异具有统计学意义(Z=4.063, 4.004, 均P<0.05)。

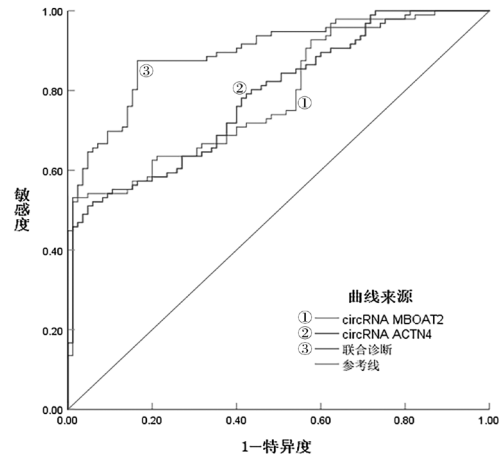


图1 circRNA MBOAT2, circRNA ACTN4 诊断胆管癌发生的 ROC 曲线

表2 circRNA MBOAT2, circRNA ACTN4 对胆管癌发生的诊断价值

项目	AUC	95%CI	P值	截断值	敏感度 (%)	特异度 (%)	阳性预测值 (%)	阴性预测值 (%)	约登指数
circRNA MBOAT2	0.784	0.717-0.841	<0.001	1.12	52.08	98.82	98.04	64.62	0.509
circRNA ACTN4	0.786	0.719-0.843	<0.001	1.17	51.04	95.29	92.45	63.28	0.463
联合诊断	0.895	0.841-0.936	<0.001	-	87.50	83.53	85.71	85.54	0.710

2.3 circRNA MBOAT2, circRNA ACTN4与患者临床病理特征的关系 见表3。以胆管癌患者circMBOAT2(1.12), circACTN4(1.17)截断值为界限, 将患者分为circRNA MBOAT2高表达组(n=47)、低表达

组(n=49)和circRNA ACTN4高表达组(n=50)、低表达组(n=46), 见表3。circRNA ACTN4与临床分期、淋巴结状态相关, 差异具有统计学意义(均P<0.05)。

表3 circRNA MBOAT2, circRNA ACTN4 与患者临床病理特征的关系 [n (%)]

类别	n	circRNA MBOAT2		χ ² 值	P值	circRNA ACTN4		χ ² 值	P值
		高表达 (n=47)	低表达 (n=49)			高表达 (n=50)	低表达 (n=46)		
年龄 (岁)	≤ 48	26 (55.32)	22 (44.90)	1.042	0.307	24 (48.00)	24 (52.17)	0.167	0.683
	>48	21 (44.68)	27 (55.10)			26 (52.00)	22 (47.83)		
性别	男	23 (48.94)	28 (57.14)	0.649	0.421	28 (56.00)	23 (50.00)	0.346	0.556
	女	24 (51.06)	21 (42.86)			22 (44.00)	23 (50.00)		
肿瘤浸润程度	黏膜层	18 (38.30)	20 (40.82)	0.064	0.801	21 (42.00)	17 (36.96)	0.255	0.614
	超过黏膜下层	29 (61.70)	29 (59.18)			29 (58.00)	29 (63.04)		
临床分期	I-II	18 (38.30)	31 (63.27)	5.984	0.014	20 (40.00)	29 (63.04)	5.091	0.024
	III-IV	29 (61.70)	18 (36.73)			30 (60.00)	17 (36.96)		
分化程度	中高分化	25 (53.19)	19 (38.78)	2.008	0.156	27 (54.00)	17 (36.96)	2.803	0.094
	低分化	22 (46.81)	30 (61.22)			23 (46.00)	29 (63.04)		
淋巴结转移	无	23 (48.94)	31 (63.27)	2.002	0.157	24 (48.00)	30 (65.22)	2.886	0.089
	有	24 (51.06)	18 (36.73)			26 (52.00)	16 (34.78)		
淋巴结状态	阴性	15 (31.91)	27 (55.10)	5.241	0.022	16 (32.00)	26 (56.52)	5.854	0.016
	阳性	32 (68.09)	22 (44.90)			34 (68.00)	20 (43.48)		
神经侵入	无	19 (40.43)	28 (57.14)	2.683	0.101	22 (44.00)	25 (54.35)	1.027	0.311
	有	28 (57.14)	21 (42.86)			28 (56.00)	21 (56.65)		
肿瘤直径 (cm)	≤ 2	22 (46.81)	29 (59.18)	1.475	0.225	23 (46.00)	28 (60.87)	2.127	0.145
	>2	25 (53.18)	20 (40.82)			27 (54.00)	18 (39.13)		

2.4 COX回归分析胆管癌患者预后的影响因素 见表4。结果显示, 淋巴结状态阳性和circRNA

MBOAT2, circRNA ACTN4高表达为患者死亡的独立危险因素, 差异具有统计学意义(均P<0.05)。

表 4

COX 回归分析胆管癌患者预后的影响因素

因素	单因素分析			多因素分析		
	β	P	HR	β	P	HR
年龄	0.241	0.346	1.273			
性别	0.294	0.515	1.342			
肿瘤浸润程度	0.423	0.249	1.526			
临床分期	0.622	0.014	1.863	0.421	0.264	1.524
分化程度	-0.375	0.232	0.687			
淋巴结转移	0.380	0.133	1.462			
淋巴结状态	0.421	0.021	1.524	0.423	0.023	1.527
神经侵入	0.486	0.134	1.627			
肿瘤直径	0.386	0.288	1.471			
circRNA MBOAT2	0.521	0.042	1.684	0.459	0.040	1.582
circRNA ACTN4	0.453	0.037	1.573	0.546	0.036	1.727

2.5 circRNA MBOAT2, circRNA ACTN4与胆管癌患者预后生存的关系 见图2, 3所示。circRNA MBOAT2高表达组患者累积生存率为23.40%, 低于circRNA MBOAT2低表达组患者的46.94%; circRNA ACTN4高表达组患者累积生存率为24.00%, 低于circRNA ACTN4低表达组的47.83%, 差异具有统计学意义($\chi^2=5.809, 5.946$, 均 $P < 0.05$)。

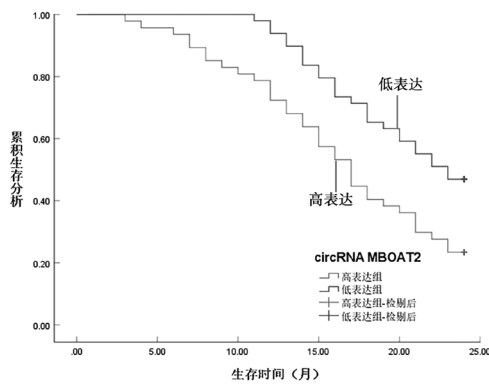


图 2 circRNA MBOAT2 与胆管癌患者预后生存的关系

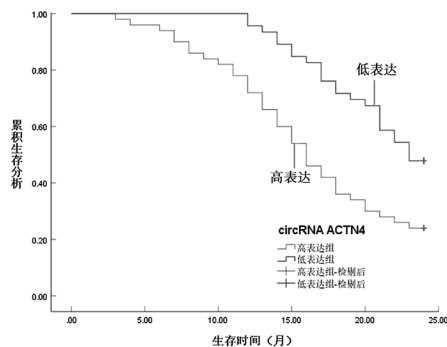


图 3 circRNA ACTN4 与胆管癌患者预后生存的关系

3 讨论

胆管癌包括一系列高度异质性的胆管恶性肿瘤, 这些肿瘤可能在胆管树的任何部位出现(肝内、肝门周和远端), 每种亚型都有不同的遗传异常、临床表现和治疗方法, 它们的发病率在全球范围内不

断上升, 且由于症状不明显, 高攻击性和对化疗的不稳定性, 导致其死亡率较高^[6]。纤维多囊性疾病(硬化性胆管炎、肝结石、肝硬化)、病毒性肝炎及与肥胖相关的脂肪肝炎等都有可能发生胆管癌, 但不管病因如何, 最终都会引起慢性炎症或胆汁淤积, 使胆管细胞更多地暴露于炎症因子(白介素-6、肿瘤坏死因子- α 等), 导致胆管细胞损伤, 肿瘤抑制基因、原癌基因等逐步突变, 从而促进肿瘤生长、血管生成和细胞迁移^[7]。在诊断时, 大多数患者多为晚期或存在转移性疾病, 治疗时不可切除, 患者得不到特定的癌症治疗, 导致预后差。因此, 需要生物标志物监测疾病进展, 降低与癌症有关的死亡率。

circRNA与微小RNA都来源于前体mRNA, 转录效率相同, 但其间接方式不同, circRNA主要通过反向剪接产生, 不同类型的circRNA分布于细胞的不同部位, 表现出不同的生物学功能^[8]。circRNA属于非编码RNA家族, 具有由头尾共价键形成的闭环结构, 缺少3'末端使其不易被核酸外切酶消化, 因此比相关的线性微小RNA更稳定。随着生物信息学技术的发展, 不同长度和类型的circRNA被发现, 研究表明, 它们在真核细胞中富集并在物种间高度保守^[9]。circRNA虽属于不编码蛋白的RNA, 但它通过充当miRNA抑制剂、蛋白质诱饵等调节基因功能, 广泛调节生理和病理过程。重要的是circRNA在癌症中表达异常, 在肿瘤发生和进展中发挥着不可或缺的作用^[10]。circRNA MBOAT2在胆管癌中明显上调, 并与疾病的恶性特征呈正相关, 敲除后则抑制癌细胞的生长和转移, 过表达则促进脂肪酸合酶的胞质输出, 改变胆管癌脂质代谢谱并调节氧化还原稳态来促进癌症进展, 表明circRNA MBOAT2可能是具有活性脂质代谢的胆管癌的有效靶点^[11]。本研究结果与之一致, circRNA MBOAT2表达随着疾病进展不断增加, 其高表达与患者临床分期III~IV期、淋巴结状态阳性相关。提示, circRNA MBOAT2可能通过改变患者脂质代谢谱参与胆管癌进

展,其水平越高,患者病理特征越明显,可通过患者病理特征及circRNA MBOAT2表达预测胆管癌发生风险。研究发现, circRNA MBOAT2能够促进癌细胞增殖、迁移和入侵,可作为新型的结直肠癌的诊断标记物判断患者预后情况^[12]。本研究中, circRNA MBOAT2表达上升是患者预后不良的独立危险因素,高表达circRNA MBOAT2患者生存率低于低表达患者。提示, circRNA MBOAT2通过促进癌细胞增殖和迁移加速癌症进展,其水平越高,患者死亡风险也越高。

ACTN4属于肌动蛋白结合家族,是一种与癌细胞运动性密切相关的非肌肉 α 肌动蛋白,参与核转录因子活性的调节以及病毒的复制,突变后会引致肾脏畸形和功能障碍。circRNA ACTN4在分子机制上影响周期和细胞迁移,参与肿瘤发展和转移^[13]。circRNA ACTN4在胆管癌中表达显著上升,通过增加YPS相关蛋白1的表达,参与体内和体外肿瘤增殖和转移,推测ACTN4可能是胆管癌一个潜在的预后标志物和治疗目标^[14]。本研究结果与之一致,胆管癌患者circRNA ACTN4水平高于结石组和对照组,并与患者临床病理特征临床分期和淋巴结状态相关。提示,可通过circRNA ACTN4水平初步判定胆管癌发生的风险。本研究还发现, circRNA MBOAT2和circRNA ACTN4呈正相关,两者联合诊断胆管癌发生具有较高的价值。提示,监测circRNA MBOAT2, circRNA ACTN4表达能够有效诊断疾病发生。据报道, circRNA ACTN4过表达显著促进了乳腺癌细胞在体内和体外的生长、浸润和转移,而对其沉默后则结果相反。它在乳腺癌组织和细胞中的表达与临床分期和患者预后不良相关^[15]。本研究中, circRNA ACTN4是患者预后不良的独立危险因素,且circRNA ACTN4高表达患者生存率显著低于低表达患者。提示, circRNA ACTN4可能通过促进癌细胞浸润和转移促进疾病进展,高表达患者死亡风险较高。

综上所述, circRNA MBOAT2, circRNA ACTN4在胆管癌患者中表达上升,联合诊断胆管癌发生具有一定的价值。同时, circRNA MBOAT2, circRNA ACTN4是患者预后不良的独立危险因素,两者高表达患者生存率较低。

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