



半乳糖凝集素-9和音猬因子表达检测在结直肠癌早期诊断及预后中的作用*

何倩¹, 刘昕¹, 林甜甜², 董笑楠^{1△}

1. 青岛大学附属青岛市海慈医院(青岛市中医医院)肛肠科(青岛 266000);

2. 青岛大学附属青岛市海慈医院(青岛市中医医院)普外科(青岛 266000)

【摘要】目的 观察结直肠癌患者癌组织中半乳糖凝集素-9(galectin-9)和音猬因子(sonic hedgehog, SHH)的表达变化,分析二者与结直肠癌发生风险及预后的关联。**方法** 回顾性纳入2020年5月-2022年5月青岛市中医医院收治的结直肠癌患者210例,检测其癌组织及癌旁组织中galectin-9与SHH的表达水平。采用logistic回归分析两者表达与结直肠癌发病风险之间的关系,并绘制受试者工作特征(receiver operating characteristic, ROC)曲线,评估二者对结直肠癌发病风险及预后的预测价值。**结果** 与癌旁组织相比,癌组织中galectin-9和SHH的表达水平差异均有统计学意义($P<0.05$)。ROC曲线分析显示,galectin-9和SHH表达水平评估结直肠癌发生风险的曲线下面积(area under the curve, AUC)分别为0.809(95% CI: 0.751 ~ 0.868)和0.865(95% CI: 0.817 ~ 0.912)。在T₃₋₄、N₁₋₃、M₁及低分化患者中galectin-9表达降低($P<0.05$),而SHH表达水平则升高($P<0.05$)。Galectin-9与SHH表达及TNM分期呈负相关($r=-0.184$ 、 -0.362 , $P<0.001$);SHH表达与TNM分期正相关($r=0.407$, $P<0.001$)。预后不良与预后良好患者galectin-9、SHH表达水平比较差异有统计学意义($P<0.05$)。Logistic回归分析显示,T₃₋₄期(OR=4.609, 95%CI: 1.461 ~ 14.535)、低分化(OR=3.337, 95%CI: 1.297 ~ 8.582)及SHH(OR=2.067, 95%CI: 1.162 ~ 3.678)水平为影响患者预后的危险因素($P<0.05$),galectin-9(OR=0.652, 95%CI: 0.437 ~ 0.975)为影响患者预后的保护因素($P<0.05$)。ROC曲线显示,galectin-9、SHH表达水平评估结直肠癌预后的AUC分别为0.769(95% CI: 0.550 ~ 0.798)和0.734(95% CI: 0.603 ~ 0.866)。**结论** Galectin-9、SHH在结直肠癌患者中分别呈低表达和高表达,其表达水平与肿瘤的低分化、侵袭和转移行为有关,且对患者患病风险和预后具有一定的评估价值。

【关键词】 结直肠癌 半乳糖凝集素-9 音猬因子 预后 预测价值

Role of Galectin-9 and Sonic Hedgehog Expressions in the Early Diagnosis and Prognosis of Colorectal Cancer

HE Qian¹, LIU Xin¹, LIN Tiantian², DONG Xiaonan^{1△}. 1. Department of Proctology, Qingdao Haici Hospital (Qingdao Traditional Chinese Medicine Hospital) Affiliated with Qingdao University, Qingdao 266000, China; 2. Department of General Surgery, Qingdao Haici Hospital (Qingdao Traditional Chinese Medicine Hospital) Affiliated with Qingdao University, Qingdao 266000, China

△ Corresponding author, E-mail: haicisxn@163.com

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[Abstract] Objective To investigate the association between the expression levels of galectin-9 and sonic hedgehog (SHH) and the risk of occurrence and prognosis in patients with colorectal cancer (CRC). **Methods** A total of 210 patients with CRC treated at Qingdao Traditional Chinese Medicine Hospital between May 2020 and May 2022 were retrospectively included. The expressions of galectin-9 and SHH in tumor tissues were measured. Logistic regression was used to analyze the relationship between galectin-9/SHH expression and CRC risk. Receiver operating characteristic (ROC) curves were plotted to evaluate the predictive value of galectin-9 and SHH for CRC risk and prognosis. **Results** The expression levels of galectin-9 and SHH differed significantly between cancer tissues and adjacent normal tissues ($P<0.05$). ROC analysis showed that the AUCs for galectin-9 and SHH in evaluating CRC risk were 0.809 (95% CI: 0.751-0.868) and 0.865 (95% CI: 0.817-0.912), respectively. Galectin-9 expression was lower in patients with T₃₋₄ stage, N₁₋₃ stage, M₁ stage, or poor differentiation ($P<0.05$), whereas SHH expression was higher in these patients ($P<0.05$). Galectin-9 expression was negatively correlated with SHH expression and TNM stage ($r=-0.184$ and -0.362 , respectively; $P<0.001$). SHH expression was positively correlated with TNM stage ($r=0.407$, $P<0.001$). Significant differences in galectin-9 and

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△ 通信作者, Email: haicisxn@163.com

SHH expression were observed between patients with poor prognosis and those with good prognosis ($P < 0.05$). Logistic regression analysis indicated that T_{3-4} stage (OR = 4.609, 95% CI: 1.461-14.535), poor differentiation (OR = 3.337, 95% CI: 1.297-8.582), and high *SHH* expression (OR = 2.067, 95% CI: 1.162-3.678) were risk factors for poor prognosis ($P < 0.05$), while high galectin-9 expression (OR = 0.652, 95% CI: 0.437-0.975) was a protective factor ($P < 0.05$). The AUCs of galectin-9 and *SHH* for evaluating CRC prognosis were 0.769 (95% CI: 0.550-0.798) and 0.734 (95% CI: 0.603-0.866), respectively. **Conclusion** Galectin-9 and *SHH* are lowly and highly expressed, respectively, in CRC. Their expression levels are associated with tumor differentiation, invasion, and metastasis, and hold predictive value for the risk and prognosis of CRC patients.

[Key words] Colorectal cancer Galectin-9 Sonic hedgehog Prognosis Predictive value

结直肠癌是仅次于乳腺癌、肺癌的高风险肿瘤,死亡率高居第二位。尤其值得关注的是,多数患者就医时已处于中晚期,预后不理想^[1-3]。因此,结直肠癌的早期筛查和预后评估是临床的重要工作内容。然而,结直肠癌的发生发展涉及复杂的分子遗传和免疫应答等诸多病理机制,目前临床仍缺乏有效的评估指标和治疗靶点^[4-7]。研究表明,半乳糖凝集素-9(galectin-9)在结直肠癌组织中存在异常表达,尤其在伴有远处转移的患者中其表达显著下调。这种低表达状态可能增强癌细胞的迁移能力,从而对患者预后造成不利影响。此外,刺猬因子(sonic hedgehog, *SHH*)作为调控干细胞自我更新的关键信号蛋白,其表达上调与肿瘤细胞的侵袭和迁移密切相关。现有证据提示,在结直肠癌中galectin-9与*SHH*之间可能存在相互作用,共同调控包括细胞凋亡在内的多种恶性生物学行为。然而,目前关于二者在结直肠癌中的具体关系尚不明确,其在预后评估中的临床价值亦缺乏充分的循证医学证据支持^[8-9]。基于上述背景,galectin-9与*SHH*的表达水平有望成为评估结直肠癌发生风险、预后判断及治疗靶点筛选的潜在生物标志物。为此,本研究旨在进一步阐明两者在结直肠癌发生发展中的作用机制,以期临床诊疗提供更为可靠的循证依据。

1 资料与方法

1.1 研究对象

回顾性纳入2020年5月-2022年5月青岛市中医医院收治的结直肠癌患者210例。纳入标准:①符合结直肠癌的临床诊断^[10],经病理检测确诊;②病理样本保存完好及其他信息资料完整;③性别不限,年龄18岁及以上;④患者及家属接受并完成随访。排除标准:①伴有炎症肠病、肠息肉、肠道感染等肠道疾病;②合并其他类型的恶性肿瘤伴肠道转移;③合并子宫内膜异位症肠道侵犯;④获取病理样本前接受放化疗等治疗者;⑤获取病理样本前接受免疫制剂、抗炎制剂等治疗者。本研究经青岛市中医医院伦理委员会批准通过(批准号:2022HC05LS015)。

1.2 方法

1.2.1 组织galectin-9表达测定

取入组患者的癌组织及癌旁组织样本50 mg,漂洗,剪碎,冰上裂解并碾磨制成组织匀浆,取组织匀浆液适量使用离心机以3 000 r/min的转速分离获得上清液,采用酶联免疫吸附法测定galectin-9水平。

1.2.2 组织*SHH*表达测定

另取样本碾磨后以Trizol法提取总RNA,逆转录cDNA,加入引物序列(5'-ACCGAGGGCTGGGACGAAGA-3', 5'-ATTTGGCCGCCACCGAGT-3')进行PCR扩增,扩增条件:95 ℃ 15 min 变性后进行40个循环扩增,每一循环包括95 ℃ 15 s, 60 ℃ 30 s, 80 ℃ 5 s。以GAPDH为内参,2^{- $\Delta\Delta C_t$} 法测定*SHH*的相对表达量。

1.2.3 随访

所有患者接受门诊或电话随访,每年随访4次(每季度一次),随访截至2024年8月,记录患者预后情况。

1.2.4 资料收集与质控

由专业医务人员从医院数据库调取患者信息,包括人口学特征、病理学资料及相关检测数据。所有资料均由两名研究人员采用双人独立录入的方式进行收集,录入后对数据进行核对、校正,确保数据准确无误。

1.3 统计学方法

采用SPSS 22.0与MedCalc软件进行统计分析。计数资料以例数与百分比(%)表示,组间比较采用 χ^2 检验;计量资料如galectin-9与*SHH*表达水平等服从正态分布,以均值 $\pm$ 标准差描述,组间比较采用 t 检验。通过Pearson或Spearman相关性分析galectin-9与*SHH*表达之间的相关性,以及二者与TNM分期的关系。采用logistic回归分析影响患者预后的相关因素。绘制受试者工作特征曲线(receiver operating characteristic, ROC),评估galectin-9与*SHH*表达对结直肠癌发病风险及预后的预测效能,以约登指数最大值为界确定最佳截断值,并计算曲线下面积(area under the curve, AUC),以 $P < 0.05$ 表示差异有统计学意义。

2 结果

2.1 患者基线资料及galectin-9和SHH表达比较

患者男性128例,占60.95%,女性82例,占39.05%;年龄52~74岁,平均(64.86±6.48)岁;中高分化126例,低分化84例;T₁₋₂期142例,T₃₋₄期68例;淋巴结转移59例;远处转移32例。癌组织galectin-9表达水平低于癌旁组织($P<0.05$),SHH表达水平高于癌旁组织($P<0.05$),见表1。

表 1 结直肠癌癌组织与癌旁组织galectin-9和SHH表达比较
Table 1 Comparison of galectin-9 and SHH expressions between colorectal cancer tissue and adjacent tissue

Tissue	<i>n</i>	Galectin-9/(pg/mL)	SHH
Cancer tissue	210	31.29 ± 6.11	1.90 ± 0.62
Adjacent tissue	210	38.95 ± 6.51	1.12 ± 0.39
<i>t</i>		12.433	15.432
<i>P</i>		< 0.001	< 0.001

2.2 Galectin-9和SHH表达评估结直肠癌发病风险

ROC曲线显示,galectin-9和SHH表达水平评估结直肠癌发生风险的AUC分别为0.809(95% CI: 0.751~0.868)和0.865(95% CI: 0.817~0.912),见表2和图1。

2.3 不同临床特征患者中galectin-9和SHH表达比较

结直肠癌患者T₃₋₄期、低分化、N₁₋₃期、M₁期galectin-

9表达低于T₁₋₂期、中高分化、N₀期、M₀期患者($P<0.05$),而SHH表达水平高于T₁₋₂期、中高分化、N₀期、M₀期患者($P<0.05$),在不同性别及年龄上galectin-9和SHH表达水平差异无统计学意义($P>0.05$),见表3。

2.4 Galectin-9和SHH表达的相关性及与TNM分期的相关性

Pearson相关性显示,galectin-9与SHH表达水平成负相关($r=-0.184$, $P=0.035$);Spearman相关性显示,galectin-9与TNM分期成负相关($r=-0.362$, $P<0.001$),SHH表达水平与TNM分期成正相关($r=0.407$, $P<0.001$)。

2.5 结直肠癌不同预后患者一般资料比较

随访期间有52例患者发生肿瘤进展或死亡(预后不良),余158例病情控制良好(预后良好),结直肠癌预后不良患者galectin-9低于预后良好患者($P<0.05$),而TNM分期3、4期、低分化占比及SHH表达水平高于预后良好患者($P<0.05$),见表4。

2.6 影响患者预后的logistic回归分析

以结直肠癌患者预后情况为因变量(预后不良=1,预后良好=0),以TNM分期(3、4期=1,1、2期=0)、分化程度(低分化=1,中高分化=0)及galectin-9和SHH为自变量,经logistic回归分析显示,3、4期、低分化及SHH水平为影响患者预后的危险因素($P<0.05$),galectin-9为影响患者预后

表 2 Galectin-9、SHH表达评估结直肠癌发病风险的ROC曲线
Table 2 ROC curves of galectin-9 and SHH expressions in assessing colorectal cancer risk

Item	AUC	SE	<i>P</i>	95%CI	Sensitivity	Specificity	Cut-off value	Youden index
Galectin-9	0.809	0.030	<0.001	0.751-0.868	0.718	0.806	35.38 pg/mL	0.524
SHH	0.865	0.024	<0.001	0.817-0.912	0.922	0.670	1.26	0.592

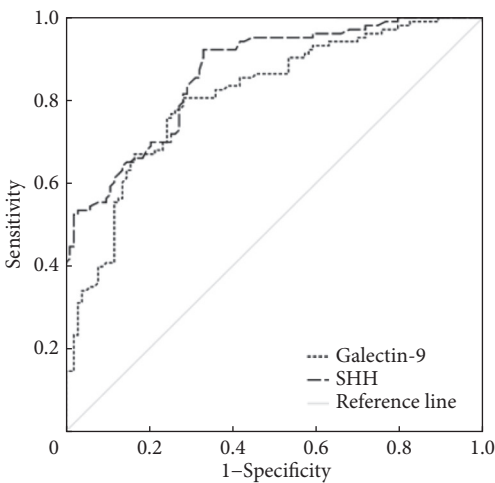


图 1 Galectin-9和SHH表达评估结直肠癌发病风险的ROC曲线
Fig 1 ROC curves of galectin-9 and SHH expressions for evaluating colorectal cancer risk

的保护因素($P<0.05$),见表5。

2.7 Galectin-9和SHH表达评估结直肠癌的预后

ROC曲线显示,galectin-9和SHH表达水平评估结直肠癌预后的AUC分别为0.769(95% CI: 0.550~0.798)和0.734(95% CI: 0.603~0.866),见表6、图2。

3 讨论

结直肠癌具有高度异质性,其复杂的病理机制为诊疗带来了较大挑战。目前尚无特效治疗方法能显著改善现有困境,因此需要持续探索其发生发展的具体途径,以期临床诊疗提供新方向^[11-13]。近年来,随着精准医学理念的深入和分子生物学技术的发展,越来越多的信号分子靶点被证实与结直肠癌的发病风险相关。这些靶点在肿瘤进展、耐药等恶性生物学行为中发挥关键作用,不仅

表 3 不同临床特征结直肠癌患者galectin-9、SHH表达情况

Table 3 Galectin-9 and SHH expresion in colorectal cancer patients with different clinical characteristics

Item	Galectin-9/(pg/mL)	<i>t</i>	<i>P</i>	SHH	<i>t</i>	<i>P</i>
T staging		4.517	< 0.001		8.514	< 0.001
T ₁₋₂ (<i>n</i> = 142)	32.42 ± 5.23			1.72 ± 0.38		
T ₃₋₄ (<i>n</i> = 68)	28.93 ± 5.26			2.28 ± 0.56		
Differentiation degree		3.743	< 0.001		6.680	< 0.001
Moderately well differentiated(<i>n</i> = 126)	32.56 ± 5.62			1.69 ± 0.47		
Poorly differentiated(<i>n</i> = 84)	29.39 ± 6.56			2.22 ± 0.68		
N staging		6.221	< 0.001		9.882	< 0.001
N ₁₋₃ (<i>n</i> = 59)	27.42 ± 6.08			2.43 ± 0.63		
N ₀ (<i>n</i> = 151)	32.80 ± 5.45			1.69 ± 0.42		
M staging		4.492	< 0.001		9.459	< 0.001
M ₁ (<i>n</i> = 32)	27.01 ± 6.47			2.63 ± 0.59		
M ₀ (<i>n</i> = 178)	32.06 ± 5.74			1.77 ± 0.45		
Gender		1.808	0.072		0.345	0.730
Male(<i>n</i> = 128)	31.90 ± 5.94			1.89 ± 0.59		
Female(<i>n</i> = 82)	30.34 ± 6.34			1.92 ± 0.65		
Age		1.096	0.274		0.937	0.350
≥ 60 yr.(<i>n</i> = 168)	32.52 ± 6.07			1.88 ± 0.65		
< 60 yr.(<i>n</i> = 42)	30.37 ± 6.13			1.98 ± 0.47		

可用于评估肿瘤的发展与预后,也有望成为未来临床干预病情的重要靶点^[14-17]。因此,探索新型肿瘤靶点已成为当前临床研究的重要任务。

本研究结果显示,在结直肠癌组织中galectin-9呈低表达,而SHH呈高表达。两者用于评估结直肠癌发病风险的AUC分别为0.809和0.865,提示这两种指标因子与结直肠癌发病风险相关,并具有一定的诊断价值。Galectin-9属于凝集素蛋白家族,参与机体免疫调节,在恶性肿瘤中可通过抑制T淋巴细胞和自然杀伤细胞的抗肿瘤作用促进肿瘤发展^[18-19]。有研究^[20]表明,在肿瘤患者中,galectin-9可受T淋巴细胞诱导,通过易位至细胞表面及自噬途径分泌至胞外,进而介导肿瘤免疫逃逸,促进肿瘤进展。然而,galectin-9在结直肠癌中的作用尚存争议。有报道^[21]指出,galectin-9在结直肠癌癌旁组织中阳性表达较高,在癌组织中表达较低,其低表达是影响患者无复发生存期和总生存期的独立危险因素(风险比=1.80)。另一研究^[22]显发现,萘环类药物诱导galectin-9上调是肿瘤免疫逃逸的新机制,而抑制galectin-9可增强肿瘤对萘环类药物的敏感性。但也有研究^[23]显示,galectin-9的表达与树突状细胞浸润相关;与CD1a⁺未成熟

树突状细胞呈负相关,与CD208⁺成熟树突状细胞呈正相关;且galectin-9高表达的患者组织中CD8⁺T细胞和CD3⁺T细胞浸润更丰富。本研究结果表明,galectin-9低表达与肿瘤T分期及转移相关,提示其低表达可能促进肿瘤恶性进展,从而影响患者预后。临床上可通过监测galectin-9水平下降情况,辅助评估结直肠癌的分化、浸润及迁移能力,进而判断肿瘤分期进展与转移风险,为及时调整治疗方案、控制病情进展提供参考。

SHH作为人体干细胞增殖、分化过程中的关键信号调控因子,同时也是一种维持肿瘤干细胞特性的重要信号分子,参与肿瘤的发生与发展过程^[24]。本研究显示,SHH在结直肠癌的高T分期、淋巴结转移及远处转移组织中呈现异常高表达,对患者不良预后具有较高的评估价值,提示SHH高表达及其信号通路的激活可促进癌细胞的侵袭和迁移能力,从而驱动肿瘤恶性进展。另有研究^[25]表明,SHH高表达的结直肠癌患者更易出现肿瘤分期进展、脉管侵犯和淋巴结转移,其机制可能与短链非编码RNA-582-5p通过靶向调控SHH表达来调控癌细胞增殖、迁移与侵袭有关。BEENA等^[26]研究指出,SHH表达与结直肠癌转移密切相关,可增加患者癌因性死亡风险;而

表 4 结直肠癌不同预后患者一般资料比较

Table 4 Comparison of general characteristics in colorectal cancer patients with different prognosis

Item	Poor prognosis(<i>n</i> = 52)	Good prognosis(<i>n</i> = 158)	χ^2/t	<i>P</i>
Sex/case (%)			0.780	0.377
Male	29(55.77)	99(62.66)		
Female	23(44.23)	59(37.34)		
Smoking/case (%)			1.222	0.269
Yes	9(17.31)	18(11.39)		
No	43(82.69)	140(88.61)		
Alcohol drinking/case (%)			2.223	0.136
Yes	13(25.00)	25(15.82)		
No	39(75.00)	133(84.18)		
TNM staging/case (%)			68.149	< 0.001
Stage 1-2	11(21.15)	131(82.91)		
Stage 3-4	41(78.85)	27(17.09)		
Differentiation degree/case (%)			31.507	< 0.001
Low differentiation	38(73.08)	46(29.11)		
Middle-high differentiation	14(26.92)	112(70.89)		
Treatment method/case (%)			4.660	0.097
Chemoradiotherapy	16(30.77)	26(16.88)		
Surgery	7(13.46)	27(17.53)		
Surgery + chemoradiotherapy	29(55.77)	101(65.58)		
Diabetes mellitus/case (%)	6(11.54)	9(5.70)	1.229	0.268
Hypertension/case (%)	9(17.31)	17(10.76)	1.546	0.214
Hyperlipidemia/case (%)	8(15.38)	19(12.03)	0.394	0.530
Age/yr., $\bar{x} \pm s$	66.15 $\pm$ 6.51	64.44 $\pm$ 6.42	1.660	0.098
Body mass index/(kg/m ²), $\bar{x} \pm s$	23.15 $\pm$ 2.48	22.76 $\pm$ 2.39	1.011	0.313
Galectin-9/(pg/mL), $\bar{x} \pm s$	28.27 $\pm$ 6.69	32.28 $\pm$ 5.61	4.256	< 0.001
SHH($\bar{x} \pm s$)	2.35 $\pm$ 0.81	1.75 $\pm$ 0.45	6.700	< 0.001

表 5 影响患者预后的logistic回归分析

Table 5 Logistic regression analysis of factors affecting patient prognosis

Item	β	SE	Wald	OR	<i>P</i>	95%CI
TNM staging(stage 1-2)	1.528	0.586	6.799	4.609	0.009	1.461-14.535
Differentiation degree (middle-high differentiation)	1.205	0.482	6.250	3.337	0.013	1.297-8.582
Galectin-9	− 0.427	0.205	4.339	0.652	0.038	0.437-0.975
SHH	0.726	0.294	6.098	2.067	0.014	1.162-3.678

The reference group is in parentheses. β : partial regression coefficient; SE: standard error; OR: odds ratio; CI: confidence interval.

激活单磷酸腺苷活化蛋白激酶可通过调节 *SHH* 通路及代谢过程影响癌症进展。此外, 亦有研究^[27]显示, *SHH* 能够调节肠上皮细胞与间质细胞之间的正反馈循环, 从而促进上皮组织增生。临床上可结合本研究中 *SHH* 表达水平的变化, 辅助评估结直肠癌的分化程度、分期进展及肿瘤转移风险, 为诊疗决策提供参考依据。

基于上述研究可知, galectin-9 与 *SHH* 在结直肠癌中

可能分别发挥抑癌和促癌作用。galectin-9 表达水平越低、*SHH* 表达水平越高, 提示肿瘤增殖、迁移等恶性行为越强, 治疗应答可能也越差。两者均为影响结直肠癌患者预后的重要因素, 其评估结直肠癌预后的 AUC 分别为 0.769 和 0.734, 截断值分别为 32.08 pg/mL 和 2.57。这表明 galectin-9 与 *SHH* 水平变化对患者治疗后病情进展及生存期等预后情况也具有一定评估价值。临床医师可结合本

表 6 Galectin-9和SHH表达评估结直肠癌预后的ROC曲线

Table 6 ROC curves for galectin-9 and SHH expressions in assessing colorectal cancer prognosis

Item	AUC	SE	P	95%CI	Sensitivity	Specificity	Cut-off value	Youden index
Galectin-9	0.674	0.063	0.008	0.550-0.798	0.769	0.519	32.08 pg/mL	0.289
SHH	0.734	0.067	< 0.001	0.603-0.866	0.462	0.987	2.57	0.449

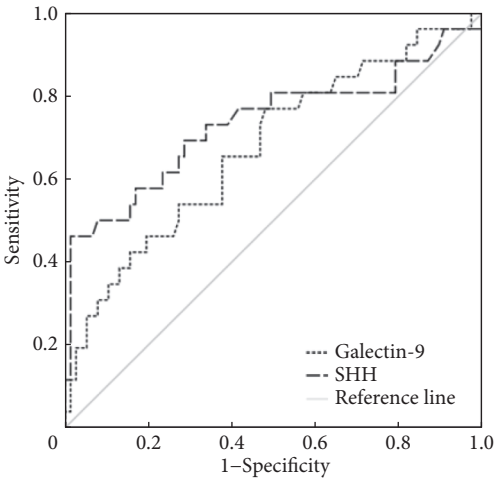


图 2 Galectin-9和SHH表达评估结直肠癌预后的ROC曲线

Fig 2 ROC curves for galectin-9 and SHH expressions in assessin colorectal cancer prognosis

研究提供的截断值数据,在治疗后对患者进行辅助筛查,以评估肿瘤进展风险及生存预后,从而可能提高临床评估的准确性。同时,该研究也提示二者可能成为未来结直肠癌诊疗的重要靶点。近年来,galectin-9在肿瘤免疫治疗领域备受关注,显示出较高的临床转化潜力。其可通过与Tim-3相互作用,调节免疫稳态与肿瘤细胞存活。研究^[28]表明,阻断Tim-3-galectin-9信号通路可减少CD8⁺T细胞凋亡,削弱肿瘤免疫逃逸,并抑制肿瘤生长。此外,galectin-9与SHH表达水平呈一定程度的弱负相关,提示二者之间可能存在相互作用或交叉调控,但具体机制尚不明确。有证据^[29]显示,上调galectin-9表达可促进结直肠癌HT29细胞凋亡,增加活化的半胱天冬酶-3蛋白水平,并降低细胞中SHH信号通路的激活水平,说明galectin-9过表达可能通过抑制SHH信号通路诱导肿瘤细胞凋亡。

综上,galectin-9低表达与SHH高表达不仅与结直肠癌患病风险升高相关,而且在肿瘤进展过程中,二者分别促进肿瘤低分化、T分期进展、淋巴结转移及远处转移,从而共同驱动肿瘤恶性进展,导致患者预后不良。因此,本研究结果可为临床医师在结直肠癌的分期、分化、转移及预后评估方面提供一定参考。然而,本研究样本量有限且为单中心数据,未来仍需通过扩大样本量、开展多中心研究并结合基础实验进一步加以验证,以期为临床

提供更精确的数据支持。

* * *

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