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临床经验 CLINICAL PRACTICE

RASSF1A基因在胃腺癌和癌前病变中的表达及意义

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■背景资料
RASSF1A是新近发现的抑癌基因, CyclinD1是细胞周期重要的调控因子. 本课题旨在研究RASSF1A及CyclinD1 mRNA在胃癌及癌前病变中的表达, 探讨RASSF1A基因与胃癌发生发展的关系.

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Expression of RASSF1A and CyclinD1 in gastric cancer and premalignant lesion and its significance

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Abstract

AIM: To investigate the role of RASSF1A and CyclinD1 in the development of gastric cancer.

METHODS: RT-PCR was used to detect the mRNA expression of RASSF1A and CyclinD1 in 20 cases of normal gastric tissues, gastric adenoma and atypical hyperplasia, and 40 cases of gastric adenocarcinoma while Western blot was adopted to detect the protein expression of RASSF1A.

RESULTS: The expression of RASSF1A was lower in gastric adenocarcinoma than in atypical hyperplasia, gastric adenoma and normal gastric tissues (37.5% *vs* 80.0%, 95.0%, 100.0%, all $P < 0.05$). However, the expression of CyclinD1 was significantly higher than in atypical hyperplasia, gastric adenoma and normal gastric tissues (77.5% *vs* 25.0%, 10.0%, 5.0%, all $P < 0.05$). In gastric cancer tissues, both of the expressions of RASSF1A and CyclinD1 mRNA were associated with pathological grade ($\chi^2 = 4.422$, $P < 0.05$; $\chi^2 = 8.935$, $P < 0.05$); their expressions were negatively correlated($r = -0.448$, $P < 0.05$), while the expressions of RASSF1A protein and mRNA were consistent.

CONCLUSION: The silent expression of RASSF1A and the increased expression of CyclinD1 may play an important role in gastric cancer pathogenesis. Their combined detection can contribute to the earlier diagnosis and treatment of gastric cancer.

Key Words: Gastric cancer; Gene; RASSF1A; CyclinD1

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摘要

目的: 探讨RASSF1A与CyclinD1在胃癌发生发展中的作用.

方法: 采用RT-PCR检测胃正常组织、腺瘤组织、不典型增生组织各20例及胃腺癌组织40例中RASSF1A及CyclinD1 mRNA的表达, 并Western blot法检测RASSF1A蛋白表达.

结果: 胃腺癌组RASSF1A的表达低于不典型增生、良性腺瘤及正常组织组(37.5% *vs* 80.0%, 95.0%, 100.0%, 均$P<0.05$), 而CyclinD1的表达高于不典型增生、良性腺瘤及正常组织组(77.5% *vs* 25.0%, 10.0%, 5.0%, 均$P<0.05$). 胃癌组织中, RASSF1A及CyclinD1 mRNA表达均与病理分级有关($\chi^2 = 4.422$, 8.935, 均$P<0.05$); 两者之间表达呈负相关($r = -0.448$, $P<0.05$); RASSF1A蛋白表达与mRNA表达一致.

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结论: RASSF1A与CyclinD1两种蛋白的异常表达在胃癌的发生发展中可能具有协同作用, 二者联合检测能为胃癌的早期临床诊断和治疗提供有利的生物学信息.

关键词: 胃肿瘤; 基因; RASSF1A; CyclinD1

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0 引言

胃癌是人类常见的恶性肿瘤, 居全球肿瘤发病和癌症死亡率的第二位[1], 胃癌的发生是一个多步骤多因素进行性发展的过程, 癌基因的激活、抑癌基因的抑制, 及其他一些肿瘤相关因子的作用, 使上皮细胞过度增殖而又不能启动凋亡信号时, 则可能逐渐发展为胃癌[2-3]. 探求相关的癌基因、抑癌基因在肿瘤发生发展中的作用, 是明确肿瘤发病机制和防治的关键因素. RASSF1A是新近发现的抑癌基因[4], CyclinD1是细胞周期重要的调控因子[5]. 本课题旨在研究RASSF1A及CyclinD1 mRNA在胃癌及癌前病变中的表达, 探讨RASSF1A基因与胃癌发生发展的关系.

1 材料和方法

1.1 材料 选取2007-01/2007-06江苏大学附属人民医院行手术切除的40例胃癌标本, 患者年龄30-85(平均57.6±13.7)岁, 均经病理确诊, 术前未用任何放、化疗, 手术时收集癌组织和距癌缘5 cm以外的癌旁正常组织, 快速置入液氮罐, 然后转入-80℃冰箱储存备用. 取同期胃癌前病变(中重度慢性萎缩性胃炎伴肠上皮化生和不典型增生)的胃镜活检标本20例, 经病理证实均为良性腺瘤, 迅速置于液氮中保存备用. RASSF1A鼠抗人mAb购自eBioscience公司, 内参GAPDH购自KangChen公司, PVD膜购自Bio-Rad公司, ECL发光试剂盒购自GE公司, PCR引物由上海生工合成.

1.2 方法

1.2.1 RT-PCR: 常规提取RNA, 行RT-PCR, 以GAPDH为内参照, 引物序列RASSF1A: F 5'-GCATGCCTGAACTACATAAC-3, R 5'-CCACAGGCCCCACTGGCCCTG-3', 扩增产物220 bp; CylinD1: F 5'-CTGCCACCCTCTTGTCTT-3', R 5'-TCCAATGGTCCAAACTGA-3'; 扩增产物326 bp; GAPDH: F 5'-GATGCCCCCATGTTCGTCATGG-3', R 5'-ACCTTGGCCAGGGGTGCTAAG-3', 扩增产物110 bp. 扩增产物置20 g/L琼脂糖电泳, 紫外灯下观察, 凝胶分析系统拍照.

1.2.2 Western blot检测: 提取组织总蛋白, 用BCA蛋白定量试剂盒测定. 等量蛋白上样, 电泳, 转PVDF膜, 封闭, TBST洗涤, 依次与一抗(1∶500)、辣根过氧化物酶(HRP)标记的羊抗鼠IgG(1∶500)反应, 化学发光法(ECL)曝光显影, 冲洗胶片, GAPDH为内参照.

统计学处理 多个样本及两样本之间比较采用χ^2检验, 两者之间相关性采用配对四格表资料相关性分析, 以$P<0.05$为差异有统计学意义.

2 结果

2.1 RASSF1A、CyclinD1 mRNA的表达 RASSF1A mRNA表达在不典型增生组低于正常组织($\chi^2 = 4.444$, $P = 0.035$), 而高于腺癌组($\chi^2 = 9.644$, $P = 0.002$); 尽管腺瘤组中有1例阴性表达, 但与正常组织组比较差异无显著性($P = 1.000$); 腺瘤组表达高于腺癌组($\chi^2 = 17.952$, $P = 0.001$), 也高于不典型增生组但差别无显著性($\chi^2 = 2.057$, $P = 0.151$); 正常组织组明显高于腺癌组表达($P = 0.001$). 腺癌中CyclinD1 mRNA表达高于不典型增生组($\chi^2 = 15.313$, $P = 0.001$), 也高于腺瘤组及正常组织组($P<0.01$); 不典型增生组高于腺瘤组($\chi^2 = 25.545$, $P = 0.001$)及正常组织组($P<0.01$); 腺瘤组与正常组织组差异无统计学差异($P>0.05$, 图1, 表1).

2.2 RASSF1A的蛋白检测 RASSF1A蛋白与mRNA表达一致, 在正常组织存在RASSF1A蛋白表达, 腺瘤组中RASSF1A mRNA表达阴性的病变中蛋白表达也阴性(图2).

2.3 RASSF1A及CyclinD1 mRNA与胃腺癌临床病理特征的关系 在胃癌组织中, RASSF1A及CyclinD1 mRNA的阳性表达与肿瘤部位、大小、TNM分期及淋巴结转移均无明显关系, 而与病理分级有关(表2).

2.4 RASSF1A与CyclinD1 mRNA在胃腺癌组织中表达的相关性 RASSF1A与CyclinD1 mRNA两者呈负相关($P<0.05$, 表3).

3 讨论

RASSF1A是新近发现的抑癌基因, 其编码产物被认为是Ras的效应物, 称之为Ras相关区域家族1(ras-association domain family-1, RASSF1),

■研发前沿
RASSF1A在恶性肿瘤的失活机制及抑制RASSF1A失活是否会对肿瘤的预防或治疗起一定作用是目前的研究重点.

■相关报道
研究发现, RASSF1A的mRNA几乎在全身所有组织中表达, 在绝大部分恶性肿瘤中表达沉默, 并认为其基因沉默在肿瘤发生中起重要作用. CyclinD1是细胞周期G_1/S期监控点重要的正向调控因子推动细胞从G_1期进入S期, 从而使细胞进入增殖状态.

■创新盛点
本研究采用RT-PCR及Western blot检测RASSF1A及CyclinD1在胃癌及癌前病变中的表达，探讨RASSF1A及CyclinD1与胃癌发生发展的关系.

表 1 RASSF1A及CyclinD1 mRNA的阳性表达

	n	RASSF1A表达		CyclinD1表达	
		n	%	n	%
癌旁正常组织	20	20	100.0	1	5.0
腺瘤组	20	19	95.0	2	10.0
不典型增生	20	16	80.0	5	25.0
腺癌	40	15	37.5	31	77.5.0

表 2 RASSF1A及CyclinD1 mRNA与胃腺癌临床病理特征的关系

	n	RASSF1A阳性表达			CyclinD1阳性表达		
		n	χ^2	P	n	χ^2	P
病变部位							
贲门	7	2			6		
胃底+胃体	11	4			9		
胃窦	22	9	0.353	0.838	16	0.676	0.713
病变大小(cm)							
≥2.5	31	12			25		
<2.5 cm	9	3	0.086	0.769	6	0.782	0.377
TNM分期							
Ⅰ–Ⅱ	15	7			9		
Ⅲ–Ⅳ	25	8	0.860	0.354	21	2.880	0.090
病理分级							
高分化	11	7			5		
中低分化	29	8	4.422	0.035	26	8.935	0.003
淋巴结转移							
有	27	11			22		
无	13	4	0.372	0.542	9	0.755	0.385

Ras GTP酶是一类分子开关超家族, 通过对细胞外信号的反应来调控细胞的增殖与调亡[4,6-11]. 研究发现, RASSF1A mRNA几乎在全身所有组织中表达, 在绝大部分恶性肿瘤中表达沉默, 并认为其基因沉默在肿瘤发生中起重要作用[12-16], 本实验发现RASSF1A基因在肿瘤中阳性表达37.5%, 明显低于在正常组织及良性腺瘤中的表达, 也高于不典型增生中的表达, 且RASSF1A基因的表达与胃腺癌的分级有关, 故推测RASSF1A基因参与了肿瘤的发生发展.

CyclinD1是细胞周期G_1/S期监控点重要的正向调控因子[17-21], 在G_1期时, 他与CDK4/CDK6结合并使之激活, 活化的CDK4/CDK6使Rb(视网膜母细胞瘤蛋白)在G_1-S转换期发生磷酸化, 释放出转录因子E2F, 进一步激活S期相关基因的转录, 推动细胞从G_1期进入S期, 从而使细胞进入增殖状态[22]. CyclinD1表达异常可引起细胞

表 3 RASSF1A与CyclinD1mRNA在胃腺癌组织中表达的关系

RASSF1A	n	CyclinD1		χ^2	P	r
		+	–			
+	15	7	8	5.974	0.015	–0.448
–	25	24	1			

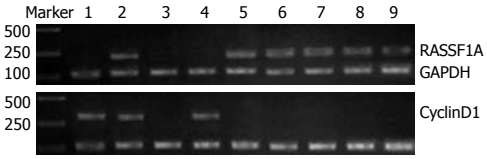

图 1 RASSF1A及CyclinD1 mRNA在胃癌组织、不典型增生组织、腺瘤组织及癌旁正常组织的表达. 1–3: 胃癌组织; 4–5: 不典型增生组织; 6–7: 腺瘤组织; 8–9: 癌旁正常组织.

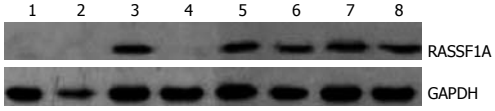

图 2 RASSF1A的蛋白在胃癌组织、不典型增生组织、腺瘤组织及癌旁正常组织的表达. 1–2: 胃癌组织; 3–4: 不典型增生组织; 5–6: 腺瘤组织; 7–8: 癌旁正常组织.

周期的失控, 是细胞异常增殖和癌变的原因. 实验结果显示, 在正常组织及腺瘤组织CyclinD1表达无明显增加, 而在不典型增生组织中表达为35%, 而在腺癌中表达高达77.5%, 提示CyclinD1表达可能与胃腺癌的发生有关, 是其重要的促发因素. CyclinD1表达与CyclinD1与胃癌的部位、大小、TNM分期及淋巴结转移无关, 但与组织学分级有关, 提示其与胃腺癌的恶性分化有关, 而与胃腺癌进展的关系尚待进一步研究.

研究发现, 在胃癌组织中RASSF1A mRN和蛋白表达水平均明显降低, 62.5%的胃癌患者中RASSF1A mRNA表达缺失或明显低下. 同时发现, 胃癌组织中RASSF1A蛋白表达明显低于癌旁正常组织, 与mRNA表达水平低下一致. RASSF1A的确切抑癌机制目前尚未清楚, 有学者推测RASSF1A可能为Ras传导通路上的Ras效应物, 扮演调控细胞负生长的角色[9,23-24]. Ras传导通路在肿瘤的发生发展中扮演重要角色, 其突变在人类30%的肿瘤中都有发现, 与GTP结合的Ras蛋白家族在信号传导过程中发挥枢纽作用. 目前已证实Ras可能与下游不同的效应分子相互作用而发挥两种截然不同的功能, 促进细胞生长和分化, 又可通过诱发细胞休眠、诱导未分化和凋亡而抑制细胞生长[12,25]. 在正常细胞中, Ras的这两种效应可通过动态的平衡维系细

胞正常代谢及生长, 而在肿瘤细胞中因甲基化引起的RASSF1A表达缺失可能使Ras更多地发挥促进生长效应而导致肿瘤发生[4,6,26-28]. 亦有学者发现, RASSF1A的外源性表达使肿瘤细胞中CyclinD1的累积明显受抑而减少, 从而阻断了由CyclinD1介导的细胞增殖通路, 使细胞周期阻断在G_1-S期[29-31], 胃腺癌中RASSF1A mRNA与CyclinD1表达呈负相关. 提示RASSF1A可能通过拮抗CyclinD1而发挥抑癌作用,

总之, 在胃腺癌中存在着RASSF1A的表达缺失和CyclinD1的高表达, 二者之间的表达具有相关性, 且表达异常在恶性组织学发生之前即已出现, 提示在胃癌前病变及腺癌中进行两者的联合检测, 能为胃腺癌的早期筛查、诊断提供有一定的帮助, 而干预RASSF1A基因的表达有可能在胃腺癌的防治中起一定作用.

■应用要点

在胃癌前病变及腺癌中进行RASSF1A及CyclinD1的联合检测, 能为胃腺癌的早期筛查、诊断提供有一定的帮助.

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■同行评价
本文提供了RASSF1A在胃癌中表达的信息, 有一定参考价值.

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