胰腺癌组织中 SKP2 和 P27 蛋白表达及其相互关系

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Expression and correlations of S-phase kinase associated protein 2 and P27 protein in pancreatic cancer tissues: an analyses of 51 cases

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Abstract

AIM: To detect the expression of S-phase kinase associated protein 2 (SKP2) and P27 protein in human pancreatic ductal carcinoma and chronic pancreatitis, and to investigate the clinical significance and their correlations in the pancreatic ductal carcinoma.

METHODS: SP immunohistochemical method was used to detect the expression of SKP2 and P27 in the routinely paraffin-embedded sections of specimens from patients with pancreatic ductal carcinoma (n = 51) and chronic pancreatitis (n = 10).

RESULTS: The positive rate of SKP2 expression in the pancreatic ductal carcinoma (28/51, 54.9%) was significantly higher than that in the chronic pancreatitis (2/10, 20.0%, P < 0.05), while the rate of P27 was significantly lower [25/51(49.0%) *vs* 9/10(90.0%), P < 0.05]. The positive rates of SKP2 expression was significantly lower in the well-differentiated (7/20, 35.0%) and non-metastasis cases (5/16, 31.2%) than those in the poorly-differentiated (14/19, 73.7%) and metastasis ones (23/35, 65.7%) (P < 0.05), while the rate of P27 expression was significantly higher in the well-differentiated (13/20, 65.0%) and non-metastasis cases (12/16, 75.0%) than those in the poorly-differentiated (6/19, 31.5%) and metastasis ones (13/35, 37.1%) (P < 0.05 or P < 0.01). The expression of SKP2 and P27 were closely correlated in the pancreatic ductal carcinoma tissue (χ^2 = 14.33, P < 0.01).

CONCLUSION: SKP2 and P27 are important biological markers for reflecting the carcinogenesis, progression, and prognosis of pancreatic ductal carcinoma. The positive expression of SKP2 or the negative expression of P27 reveals more serious status of the illness, the tendency of metastasis and unfavorable prognosis. There may be a co-regulatory relationship between SKP2 and P27 expression.

Key Words: Pancreatic carcinoma; S-phase kinase-associated protein 2; P27 protein; Immunohistochemistry

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摘要

目的: 研究胰腺导管癌和慢性胰腺炎组织中(S期激酶相关蛋白-2)SKP2和P27表达, 探讨其临床病理意义及两者在胰腺导管癌中表达的相互关系.

方法: 51例胰腺导管癌和10例慢性胰腺炎手术切除标本常规制作石蜡包埋切片, SKP2和P27染色方法为SP免疫组化法.

结果: 51例胰腺导管癌SKP2阳性表达28例 (54.9%) 和P27阳性表达25例 (49.0%), 10例慢性胰腺炎SKP2阳性2例(20.0%)和P27阳性9例(90.0%), 两者之间均存在显著差异(P<0.05), 高分化腺癌(7/20, 35.0%)和未转移(5/16, 31.2%)病例SKP2表达阳性率明显低于低分化腺癌(14/19, 73.7%)和转移(23/35, 65.7%)病例, 均存在显著差异(P<0.05); 高分化腺癌(13/20, 65.0%)和未转移(12/16, 75.0%)病例P27表达阳性率明显高于低分化腺癌(6/19, 31.5%)和转移(13/35, 37.1%)病例, 有显著或高度显著差异(P<0.05或P<0.01). SKP2和P27在胰腺导管癌中表达呈密切相关(χ^2 = 14.33, P<0.01).

结论: SKP2和P27表达是反映胰腺导管癌发生, 发展及预后的重要生物学标记物, SKP2阳性表达或P27阴性表达者恶性度高、易发生转移及预后不良, 且两者表达存在相互调控作用.

关键词: 胰腺肿瘤; S期激酶相关蛋白-2; P27蛋白; 免疫组织化学

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0 引言

S期激酶相关蛋白-2(SKP2)属于F-box蛋白家族成员, 可与cyclinA-CDK复合体相互作用, 是细胞G1期向S期转化所必需[1]. 新近研究发现SKP2表达与多种恶性肿瘤发生、发展及预后有密切关系[1-6]. P27蛋白, 又称激酶抑制蛋白1(Kip1), 是能够结合cyclin-CDK2复合体的一种多肽分子[7-8]. 近年研究发现P27表达状况也与多种恶性肿瘤发生、发展及预后有密切关系[4,8-12]. 在许多恶性肿瘤中SKP2和P27表达呈密切负相关[13-16]. 我们应用免疫组化方法研究人类胰腺导管癌和慢性胰腺炎组织中SKP2和P27表达特征, 探讨其临床病理意义及在胰腺癌表达中的相互关系.

1 材料和方法

1.1 *材料* 我院及湘雅医院胰腺癌手术切除标本51例, 男38例, 女13例, 年龄21-73(51±17)岁; 均为胰腺导管腺癌, 包括高分化腺癌20例, 中分化腺癌12例和低分化腺癌19例; 临床和(或)病理证实发生胰腺外转移(包括区域淋巴结、网膜、邻近组织器官等)35例(68.6%). 另收集我院慢性胰腺炎手术切除标本10例, 男7例, 女3例, 年龄35-55(44±10)岁. 标本经40 g/L甲醛固定后常规制作石蜡包埋切片, 切片厚4 μm. HE染色复述病理组织学特征, 其他切片行SP免疫组化染色. 鼠抗人SKP2和P27单克隆抗体, 鼠SP试剂盒及DAB-HCL显色试剂盒均购自北京中杉金桥生物公司.

1.2 *方法* SKP2和P27表达染色均为常规SP免疫组化法, 细胞质内出现明显棕黄色颗粒者为阳性细胞, 以切片中阳性细胞率≥25%为阳性病例, <25%为阴性病例[17-19]. 以北京中杉金桥生物公司提供的阳性切片作为阳性对照, 以0.01 mol/L PBS液(pH7.4)替代一抗作为每次染色的阴性或替代对照.

统计学处理 采用SPSS10.0软件包进行χ^2检验或Fishers精确概率法, 检验水准 $\alpha = 0.05$.

2 结果

SKP2和P27免疫反应阳性物质定位于细胞质, 偶见细胞核着色, 两者在癌组织中分布呈较明显异质性, 同一切片不同视野阳性细胞率及着色程度可有较明显不同. 胰腺癌51例SKP2和P27阳性病例分别为28例(54.9%)和25例(49.0%), 慢性胰腺炎10例SKP2和P27阳性病例分别为2例(20.0%)和9例(90.0%), 胰腺癌SKP2阳性率明显高于慢性胰腺炎($P<0.05$), 而胰腺癌P27阳性率明显低于慢性胰腺炎($P<0.05$); SKP2阳性和(或)P27阳性慢性胰腺炎导管上皮均呈中至重度不典型增生. 高分化腺癌和未转移病例SKP2阳性率均明显低于低分化腺癌和转移病例($P<0.05$), 而高分化腺癌和未转移病例P27阳性率均明显高于低分化腺癌和转移病例($P<0.05$或$P<0.01$)(表1). SKP2和P27表达与胰腺癌患者年龄、性别及就诊前病程等其他临床病理特征均无明显关系($P>0.05$). 28例SKP2阳性胰腺癌病例中P27阳性7例(阳性符合率25.0%), 23例SKP2阴性病例中P27阴性5例(阴性符合率21.7%), 两者表达呈密切负相关($\chi^2 = 14.33$, $P<0.01$).

表1 SKP2和P27表达与胰腺癌分化程度和转移状况的关系

特征	*n*	SKP2阳性 (%)	P27阳性(%)
高分化	20	7 (35.0)	13 (65.0)
中分化	12	7 (58.3)	6 (50.0)
低分化	19	14 (73.7)[a]	6 (31.5)[a]
无转移	16	5 (31.2)	12 (75.0)
有转移	35	23 (65.7)[a]	13 (37.1)[b]

[a]$p<0.05$, [b]$P<0.01$ *vs* 高分化或无转移

3 讨论

SKP2可与细胞周期素A-细胞周期素依赖性激酶2复合体相互作用, 调控细胞G1-S转化[1]. 在正常组织中, 脾、扁桃体、胎盘和结肠等组织呈阳性表达, 但未发现在正常胰腺导管上皮及腺泡细胞中表达. 新近, 研究发现SKP2在恶性肿瘤中表达广泛, 如胃癌、肠癌、肝癌、肺癌、乳腺癌及前列腺癌等, 而其相应正常组织除结肠黏膜外多呈阴性表达[1-6, 11, 13-18]. 进一步研究发现SKP2表达与大多数恶性肿瘤发生、进展、转移及预后有密切关系, 与阴性恶性肿瘤比较, 阳性表达者进展快, 易发生转移和复发及预后差[2-4, 6, 11, 17-29]. 本组资料发现胰腺导管癌SKP2表达阳性率明显高于慢性胰腺炎, 2例慢性胰腺炎阳性病例导管上皮呈中度和重度不典型增生各1例; 高分化和未转移胰腺导管癌SKP2阳性率明显低于低分化腺癌和转移病例. 其结果与国外文献报道较一致, 提示SKP2表达与胰腺导管癌发生、进展、转移及预后有密切关系, 阳性表达者恶性度高和易发生转移, SKP2可能是评估胰腺导管癌预后的重要生物学标记物.

P27为一种参与细胞周期调控的重要抑癌基因, 它通过调定活化细胞周素依赖性激酶2所需的细胞周期素E的阈值来抑制细胞增殖, 是一种细胞周期调节因子. 近年研究发现P27表达水平与恶性肿瘤发生及预后有密切关系, 如胃癌、肺癌、乳腺癌、前列腺癌等[4, 7-18]. 免疫组化和原位杂交研究发现部分恶性肿瘤P27及其mRNA呈阴性

表达, 而其相应正常组织及其良性病例P27多呈阳性表达, 且阴性表达的恶性肿瘤进展快、易发生转移和复发及预后差[4, 7-14, 16-18, 21-23, 27, 29-30]. 本组资料发现胰腺导管癌P27表达阳性率明显低于慢性胰腺炎, 1例阴性表达慢性胰腺炎导管上皮呈重度不典型增生; 高分化和未转移病例P27表达阳性率明显高于低分化和转移病例. 提示P27阳性表达的胰腺导管癌多恶性度低和不易发生转移, P27表达可能是反映胰腺导管癌发生、进展、生物学行为和预后的重要生物学标记物.

国外大多数学者研究发现恶性肿瘤SKP2和P27表达水平呈密切负相关, 认为其机制与两者生物学作用有关, 两者从相反方面调控细胞周期素激酶活性[13-16,29]. 本组资料发现胰腺导管癌中两者表达呈高度不一致性, 也提示存在着密切负相关.

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