

壶腹癌组织中P-gp、LRP的表达及其意义

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Expression and clinical significance of P-glycoprotein and lung resistance related protein in carcinoma of ampulla

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Abstract

AIM: To explore the expression and clinical significance of P-glycoprotein (P-gp) and lung resistance related protein (LRP) in the carcinoma of ampulla.

METHODS: Immunohistochemistry was used to detect the expression of P-gp and LRP in the tissues from 39 patients with the carcinoma of ampulla and 10 normal controls. The results and pathological features were comparatively analyzed by statistical methods.

RESULTS: The positive expression of P-gp and LRP in the tissues from the carcinoma of ampulla was significantly higher than that in the normal controls (66.7%, 59.0% vs 20%, 10%, $P < 0.05$). The expression of P-gp and LRP had no relations with the sex, age, tumor size, and clinical stages. The expression of P-gp was positively correlated with lymph node metastasis (metastasis vs non-metastasis: 80.0% vs 42.9%, $P < 0.05$). The expression of LRP was significantly higher in the highly differentiated adenocarcinoma than that in the poorly differentiated adenocarcinoma (77.8% vs 42.9%, $P < 0.05$).

CONCLUSION: P-gp expression is correlated with the metastasis potential of the ampulla carcinoma, and LRP expression is correlated with the biological features of the ampulla carcinoma.

Key Words: P-glycoprotein; Lung resistance related protein; Carcinoma of ampulla; Immunohistochemistry

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摘要

目的: 探讨壶腹癌P-gp、LRP的表达及其意义。

方法: 用免疫组化染色方法检测39例壶腹癌和10例正常壶腹P-gp、LRP表达的情况,并结合临床病理特征进行统计分析。

结果: P-gp和LRP在壶腹癌组织中的表达均高于正常壶腹组织(66.7%, 59.0% vs 20%, 10%, $P < 0.05$)。壶腹癌P-gp、LRP表达与患者性别、年龄、肿瘤直径、临床分期无关;而有淋巴结转移的壶腹癌中P-gp表达率为80.0%,明显高于无淋巴结转移的壶腹癌中P-gp表达率42.9% ($P < 0.05$);而LRP在高分化腺癌中表达率为77.8%,高于低分化腺癌42.9% ($P < 0.05$)。

结论: P-gp高表达与壶腹癌转移潜能有关,LRP与壶腹癌生物学特性有关。

关键词: P-糖蛋白; 肺耐药相关蛋白; 壶腹癌; 免疫组化

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0 引言

目前化疗仍然是肿瘤辅助治疗的重要手段之一,但肿瘤细胞多药耐药现象(multidrug resistance, MDR)是严重阻碍化疗药物在肿瘤治疗中应用的主要原因。在肿瘤细胞多药耐药的机理中,P-糖蛋白(P-glycoprotein, P-gp)、肺耐药相关蛋白(lung resistance related protein, LRP)的过度表达占有重要地位。我们应用免疫组织化学染色方法检测壶腹癌及正常壶腹中P-gp、LRP的表达,探讨其在壶腹癌组织中表达的临床意义。

1 材料和方法

1.1 材料 1998/2005在南方医科大学附属南方医院行胰十二指肠手术切除标本的病例39例, 术后病理证实为壶腹腺癌. 其中男22例, 女17例, 年龄33-73岁, 平均 57 ± 9 岁, 术前均未用过化疗. 肿瘤分化程度: 高分化腺癌18例, 中低分化腺癌21例. 肿瘤直径 ≤ 2 cm 8例, > 2 cm 31例. 淋巴结转移: 阳性25例, 阴性14例. 按2002年国际抗癌联盟(UICC)TNM临床分期: I、II期共28例, III、IV期共11例. 另取尸体标本的正常壶腹组织10例作对照.

1.2 方法 标本用40 g/L甲醛固定、石蜡包埋, 制备成4 μ m厚切片, 而后用免疫组化(S-P法)染色检测壶腹癌组织和正常壶腹组织中的P-gp、LRP表达. 抗P-gp、LRP鼠抗人单克隆抗体及免疫组织化学染色试剂盒均购于北京中山生物技术有限公司. 染色程序按试剂盒说明书进行. 以已知胰腺癌阳性片为阳性对照, 以PBS代替一抗为阴性对照. 免疫组化结果判断标准: 细胞出现棕黄色染色为阳性细胞, 高倍物镜下每张切片随机选取5个视野, 每个视野内观察100个细胞, 阳性细胞 $\geq 10\%$ 为阳性, 否则为阴性.

统计学处理 采用SPSS10.0统计软件行 χ^2 检验及Spearman等级相关分析法.

2 结果

2.1 P-gp在正常壶腹和壶腹癌中的表达 主要定位于在细胞膜, 部分位于细胞质(图1A-B). LRP在正常壶腹和壶腹癌中的表达: 主要定位于细胞质, 部分位于细胞膜(图2A-B). 壶腹癌组织中P-gp的阳性表达率为66.7%

(26/39), 高于正常壶腹组织中P-gp的阳性表达率为20.0% ($P < 0.05$). 壶腹癌组织中LRP的阳性表达率为59.0% (23/39), 正常壶腹组织中LRP的阳性表达率为10.0% (1/10), 其差异有统计学意义($P < 0.05$).

2.2 壶腹癌P-gp表达与患者性别、年龄、肿瘤分化程度、肿瘤直径、临床分期无相关性($P > 0.05$); 但是P-gp在有淋巴结转移的壶腹癌中的表达率为80.0%, 明显高于无淋巴结转移的壶腹癌中的表达率42.9% ($P < 0.05$). 壶腹癌LRP表达与患者性别、年龄、肿瘤直径、临床分期、淋巴结转移无相关性($P > 0.05$); LRP在高分化腺癌中表达率为77.8%, 高于低分化腺癌42.9%, 随肿瘤分化程度下降而下降($P < 0.05$)(表1).

表1 P-gp、LRP在壶腹癌组织中的表达

| 分组 | <i>n</i> | P-gp阳性表达 (%) | LRP阳性表达 (%) |
|-------------|----------|------------------------|------------------------|
| 性别 | | | |
| 男 | 22 | 14 (63.6) | 12 (54.5) |
| 女 | 17 | 12 (70.6) | 11 (64.7) |
| 年龄(岁) | | | |
| ≤ 60 | 23 | 16 (69.6) | 15 (65.2) |
| > 60 | 16 | 10 (62.5) | 8 (50.0) |
| 分化程度 | | | |
| 高分化腺癌 | 18 | 10 (55.6) | 14 (77.8) ^b |
| 中低分化腺癌 | 21 | 16 (76.2) | 9 (42.9) |
| 肿瘤直径 | | | |
| ≤ 2 cm | 8 | 5 (62.5) | 4 (50.0) |
| > 2 cm | 31 | 21 (67.7) | 19 (61.3) |
| TNM分期 | | | |
| I+II | 28 | 19 (67.9) | 17 (60.7) |
| III+IV | 11 | 7 (63.6) | 6 (54.5) |
| 淋巴结转移 | | | |
| (-) | 14 | 6 (42.9) | 8 (57.1) |
| (+) | 25 | 20 (80.0) ^a | 15 (60.0) |

^a $P < 0.05$, $\chi^2 = 5.571$ vs 淋巴结转移(-); ^b $P < 0.05$, $\chi^2 = 4.885$ vs 中低分化腺癌.

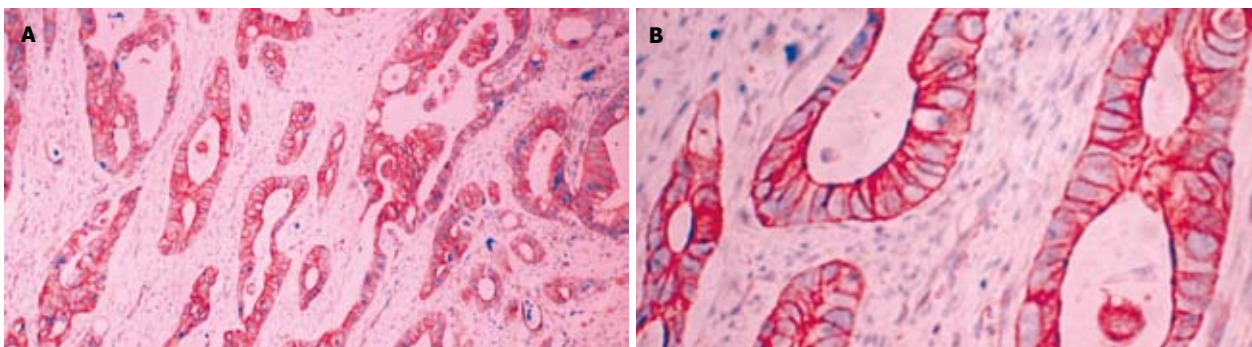


图1 P-gp在壶腹癌中的表达. A: $\times 100$; B: $\times 400$.

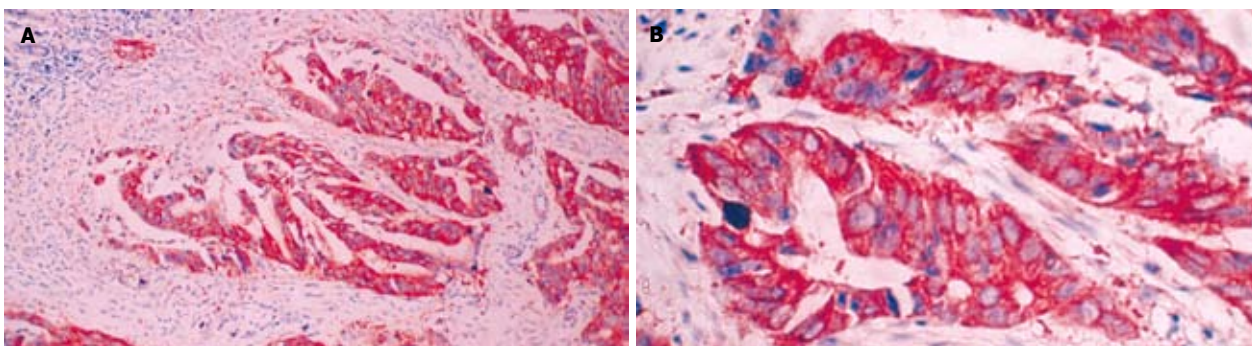


图2 LRP在壶腹癌中的表达. A: $\times 100$; B: $\times 400$.

2.3 P-gp和LRP在壶腹癌组织中的表达根据Spearman相关分析未发现两者有相关性。

3 讨论

P-gp基因定位于人类7号染色体的q21.1. 是ABC(ATP binding cassette family)超家族跨膜转运蛋白的一员. P-gp跨膜结构具有能量依赖性 " 药泵 " 的功能, 它能将抗肿瘤药物逆浓度从细胞内主动转运至细胞外, 降低细胞内药物浓度而导致肿瘤耐药^[1].

LRP最早从肺癌细胞中分离得到, 基因定位在16p11.2, 属于细胞质穹隆蛋白. LRP广泛分布于细胞器上, 它是细胞核与细胞质物质运输的通道, 构成核孔复合物的中心塞子或物质转运载体, 调控细胞核和细胞质物质的交换. LRP引起MDR的机制为: LRP阻止以胞核为效应点的药物转运到细胞质中; 将进入细胞质的药物转运到运输囊泡中, 隔绝药物作用, 并以胞吐的方式排出体外, 从而产生耐药^[2].

目前研究表明P-gp高表达多与肿瘤转移潜能、化疗疗效差、低缓解率、高复发率、生存期短等有关, 可作为肿瘤患者预后的评价指标之一^[3-6]. 本组壶腹癌P-gp表达与患者性别、年龄、肿瘤分化程度、肿瘤直径、临床分期无相关性, 而在有淋巴结转移的患者中P-gp表达阳性率明显高于无转移的患者, 提示P-gp高表达与壶腹癌的转移潜能存在一定的关系. LRP高表达同样提示肿瘤化疗疗效差、缓解率低及预后不良^[7-9], LRP在本组壶腹癌病例中的表达随肿瘤分化程度下降表达有下降趋势, 与其他因素无相关性, 表明LRP与壶腹癌生物学特性有关. Schneider *et al*^[10]研究发现联合P-gp和LRP的表达情况可以有助于判断预后.

因为P-gp和LRP涉及不同的抗肿瘤耐药谱^[11-12], 而维拉帕米、PAK-104P等许多药物可以通过抑制P-gp或LRP功能而逆转肿瘤细胞多药耐药, 提高化疗治愈率^[13-17], 我们认为通过联合检测壶腹癌P-gp、LRP表达的情况, 临床上可根据其耐药谱制定合理有效的化疗方案和有针对性使用MDR逆转剂提高化疗的疗效和治愈率; 同时为我们对壶腹癌患者的预后判断提供一定的参考价值.

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