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胃癌 P 一糖蛋白表达与化疗效果相关

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Relationship between expression of P-glycoprotein and efficacy of chemotherapy in gastric cancer

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Abstract

AIM:To investigate the significance of the expression of P-glycoprotein and the relationship between its expression and the efficacy of chemotherapy in patients with gastric cancer.

METHODS:P-glycoprotein was examined by immunohistochemical staining in 101 specimens of paraffin embedded gastric cancer tissues.

RESULTS:The expression rates of P-glycoprotein in normal gastric mucosa, paracancerous tissues and gastric cancer tissues were 13 %, 22% and 43 %, respectively(P <0.05). The expression rates of P-glycoprotein in the highly and moderately differentiated tumors (58 % and 80 %, respectively) were significantly higher than those in the lowly and poorly differentiated tumors (36 % and 25 %, respectively) (P <0.01).The postoperative cumulative survival rate of the patients receiving chemotherapy was significantly higher than that of the patients without chemotherapy in P-glycoprotein-negative patients with gastric cancer (P <0.01).

CONCLUSION:The expression of P-glycoprotein was correlated with the degree of tumor differentiation and influenced the efficacy of postoperative chemotherapy.

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摘要

目的:分析P-糖蛋白表达的临床意义，其表达与化疗疗效的关系，通过检测P-糖蛋白的表达而指导临床对胃癌患者的化疗.

方法:应用SP免疫组化方法检测101例胃癌石蜡标本，79例胃癌旁组织,15例正常胃组织.

结果:P-糖蛋白在正常胃黏膜、胃癌旁组织、胃癌组织中的表达分别为13 %,22 %,43 %,P <0.05.P-糖蛋白的表达在高分化、中分化胃癌中(58 %,80 %)显著高于低分化、未分化胃癌(36 %,25 %)，P <0.05.P-糖蛋白阴性组有化疗患者和无化疗患者两组的术后累积生存率有显著差异,P <0.01.

结论:P一糖蛋白的表达与胃癌的分化程度有关，影响术后化疗疗效.

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0 引言

多药耐药(multidrug resistance，MDR）是导致胃癌对抗肿瘤药物产生耐药的重要原因之一[1-5].他编码的P一糖蛋白(p-glycoprotein，P-gp)是一种能量依赖性药物排出泵，通过ATP提供能量,可将抗肿瘤药物由胞内泵出胞外,使其细胞毒作用减弱或消失而出现耐药性[6-10].我们检测P-gp在胃癌中的表达，分析表达的临床意义，表达与化疗疗效的关系.

1 材料和方法

1.1 材料 随机抽取胃癌石蜡标本101例，胃癌旁组织79例，其中88例胃癌患者已知其生存期.再随机抽取正常胃组织标本15例作为对照.

1.2 方法 采用SP(streptacidin 一 peroxidose，链霉菌抗生物素蛋白一过氧化物酶)方法.DAB染色，用PBS代替一抗作阴性对照，已知P-gp阳性结肠癌标本作为阳性对照.P-gp单抗购自福州迈新公司，结果判断以细胞膜上和（或）细胞质内出现棕黄色染色为阳性细胞，整张切片中阳性细胞数占≥5 %即为阳性.

统计学处理 计数资料率的比较使用χ^2检验，计量资料两组均数的比较使用t检验，累积生存率的比较使用Log-rank检验.

2 结果

胃癌组织P-gp阳性率显著高于正常胃黏膜(42.6 % vs 13.3 %,P <0.01)和胃癌旁组织(42.6 %vs 21.5 %,P <0.05)但在正常胃黏膜与胃癌旁组织间无显著差异(13.3 % vs

21.5 %,P >0.05).P-gp 的表达与胃癌患者的性别、年龄、肿瘤部位、肿瘤大小、大体类型无关(P >0.05).

2.1 P-gp 与 TNM 分期、肿瘤病理的关系 P-gp 的表达与肿瘤浸润深度、淋巴结转移、远处转移、TNM 分期无关(P >0.05).P-gp的表达与胃癌病理学类型无关(P >0.05, 表 1)，但与肿瘤分化程度相关(r = 0.24,P <0.01).即分化程度差的胃癌其 P-gp 表达率降低.

表 1 P-gp 与肿瘤病理学关系

病理	*n*	P-gp		
		阳性	阴性	阳性率 %
管状腺癌	22	15	7	68
低分化腺癌	59	22	37	37
黏液细胞癌	5	1	4	20
黏液腺癌	11	4	7	36
未分化癌	4	1	3	25
肿瘤分化				
高	12	7	5	58[b]
中	10	8	2	80
低	75	27	48	36
未	4	1	3	25

[b]P <0.01,vs 组内.

2.2 P-gp 与术后化疗的关系 有术后化疗者共 58 例，使用化疗药物以氟脲嘧啶类化疗药(包括 5-Fu,UFT, FTL，FT207)与生化调节剂醛氢叶酸为主，其余化疗药包括阿霉素、丝裂霉素、铂类等.经 Log-rank 检验，显示P-gp阴性组有化疗和无化疗两组术后累积生存率有显著差异(P <0.01,表2).有化疗组术后累积生存率高于无化疗组.P-gp阳性组有化疗和无化疗两组术后累积生存率无显著差异(P >0.05).

表 2 P-gp 与术后累积生存率(%)

T/mo	P-gp 阴性		P-gp 阳性	
	化疗组(*n* =27)	无化疗组(*n* =21)	化疗组(*n* =31)	无化疗组(*n* =9)
12	59[b]	24	39	42
24	44[b]	12	25	21
36	27[b]	6	17	14
48	13[b]	6	8	0

[b]P <0.01,vs 无化疗组.

3 讨论

我们发现P-gp在胃癌中的表达高于正常胃黏膜及胃癌旁组织,其表达与胃癌的生物学行为无关,与文献[11-13]报道相符，P-gp 的表达与分化程度相关，高、中分化胃癌表达高于低、未分化[14-16].此种现象可以说明，对于分化差的胃癌患者化疗较敏感，而分化较好的胃癌患者化疗不敏感[15].P-gp的表达是导致胃癌产生耐药的原因之一，我们通过对胃癌组织切片 P-gp 的检测，发现P-gp阴性组有术后化疗患者的术后累积生存率显著高于无术后化疗组，而P-gp阳性组的术后化疗患者与无术后化疗患者的术后累积生存率无显著差异.由此推测不表达P-gp的患者由于对化疗较敏感，所以化疗能提高生存率，而P-gp阳性的患者由于已存在原发性耐药，对化疗药物不敏感，所以即使进行术后化疗，亦不能提高生存率[16－21].同理，对于不表达 P-gp 的患者，在术后化疗过程中是否会产生继发性耐药?如果我们能对胃癌患者在化疗前后行P-gp检测则能进一步说明这个问题.

当 P-gp 表达阳性者，是否就不予化疗?近年来对 P-gp 研究的深入,发现能逆转 P-gp 的耐药方法有:(1)抑制 P-gp 的功能，使其作用下降或不能发挥作用，包括钙通道阻滞剂[22,23]，抗雌激素药[24,25]，环胞霉素[26]，或用免疫治疗的方法，如用某种 P-gp 抗体封闭 P-gp，从而改变 MDR 细胞对化疗药物的主动外排功能，逆转细胞的耐药性[27].(2)降低蛋白的合成，如调节蛋白激酶 PKA 的活性,抑制 mdr 的转录,使 P-gp 合成降低[28，29].(3)针对转录水平,即mRNA水平,如用反义核酸在mRNA水平减少相应蛋白质的表达,或用核酶直接切割靶RNA,阻断其表达，达到抑制蛋白产物产生的目的[30-32].钙通道阻滞剂维拉帕米(VER)已被用于临床[33].但其心血管系毒副作用，限制了他的用量以及在临床中的应用[34].尽管P-gp的表达影响化疗的效果，但多药耐药的机制是多样且复杂的.

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