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幽门螺杆菌相关性胃疾病胃蛋白酶原C的表达研究

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Expression of pepsinogen C in *Helicobacter pylori*-associated gastric lesions

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Abstract

AIM: To investigate the expression of pepsinogen C and its relation with *H pylori* infection in gastric cancer and precancerous lesions.

METHODS: The method of immunohistochemistry was used to examine the expression of pepsinogen C in 318 cases of stomach mucosa; the *H pylori* infection was determined by H-E stain, PCR and ELISA.

RESULTS: The rate of PGC over-expression in group of superficial gastritis of *H pylori* infection was higher than that of non-infection (P <0.05, 28/33 *vs* 15/25). The positive rate of PGC in group of atrophic gastritis of *H pylori* infection was lower than that of non-infection (P <0.01, 4/61 *vs* 9/30) and so were in dysplasia and gastric cancer.

CONCLUSION: There is a relationship between the *H pylori* infection and the expression of PGC in gastric mucosa. The expression of PGC increases in superficial gastritis and decreases in atrophic gastritis, dysplasia and gastric cancer with *H pylori* infection.

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摘要

目的: 探讨幽门螺杆菌(*H pylori*)相关性胃疾病胃蛋白酶原C的表达及其意义.

方法: 采用免疫组织化学染色法检测318例胃黏膜标本中胃蛋白酶原C的表达情况; 采用HE染色、ELISA及PCR方法检测 *H pylori*感染情况.

结果: *H pylori* 阳性组浅表性胃炎胃蛋白酶原C抗原的过表达率高于 *H pylori* 阴性组 (P <0.05, χ^2=0.032, 28/33 *vs* 15/25), *H pylori* 阳性组萎缩性胃炎胃蛋白酶原C的表达率低于 *H pylori* 阴性组(P <0.01, χ^2=0.003 4/61 *vs* 9/30), *H pylori* 阳性组的异型增生和胃癌胃蛋白酶原C的表达率与 *H pylori* 阴性组相比有下降趋势(P >0.05).

结论: *H pylori* 感染与胃蛋白酶原C的表达密切相关, 在胃黏膜炎症中胃蛋白酶原C的表达增加; 在萎缩性胃炎、异型增生和胃癌中胃蛋白酶原C的表达降低.

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0 引言

幽门螺杆菌(*H pylori*)与胃癌的发生发展关系密切[1-3], 已被列为Ⅰ类致癌因子, 但 *H pylori* 感染在胃癌发生中的作用机制目前还不甚明确. 胃蛋白酶原C是胃黏膜细胞分化成熟的终末产物, 他的变化可以反映胃黏膜的功能状态, 与胃癌及胃癌前疾病密切相关[4-8], 胃蛋白酶原与 *H pylori* 感染的关系是近年来的研究热点. 我们利用从辽宁省庄河胃癌高发区普查中获得的不同类型胃黏膜活检标本观察胃蛋白酶原C的表达, 探讨 *H pylori* 感染对胃蛋白酶原C表达的影响及其意义.

1 材料和方法

1.1 材料 1997/2002年辽宁省庄河市胃癌高发区普查中获得的318例胃黏膜活检组织, 均由病理医师进行诊断. 包括浅表性胃炎58例, 萎缩性胃炎91例(均伴有肠上皮化生), 异型增生59例, 胃癌110例. 正常对照组与病例组在性别及年龄构成上无统计学差异. 抗胃蛋白酶原C抗体(anti-pepsinogen C antibody, 商品名2D5)由日本临床检验研究所惠赠; 免疫组化用SP二步法试剂盒为福建迈新公司产品(Lot No:Kit-9801D2); ELISA试剂盒购于华美公司; *H pylori* 基因PCR试剂盒购于上海复华公司.

1.2 方法 采用HE染色、ELISA检测 *H pylori* -IgG抗体、PCR检测 *H pylori* DNA三种方法检测 *H pylori*,

同时具备三项中二项阳性者诊断为 *H pylori* 感染阳性. 胃蛋白酶原C的免疫组织化学染色(SP二步法)按说明书进行操作. 结果判定采用综合评分法[GUT 1985;26:1319-1321]: 根据细胞着色强度及阳性细胞数积分，积分数进行4级评分: 0分为阴性(-); 2-3分为(+); 4分为(++); 5-6分为(+++)大于或等于2分(+)为阳性表达; 大于或等于4分(++～+++)为过表达或强阳性.

统计学处理 利用SPSS 11.0统计软件包进行统计学处理，采用 χ^2 检验.

2 结果

318例胃黏膜活检组织按有无 *H pylori* 感染分组，*H pylori* 阳性组192例，*H pylori* 阴性组126例. 浅表性胃炎胃黏膜无论 *H pylori* 感染与否PGC抗原均为阳性表达(100%)，但 *H pylori* 阳性组PGC过表达率高于阴性组，差异显著(P <0.05，图1). 本组病例中萎缩性胃炎均伴有肠上皮化生，肠化腺体的PGC均为阴性表达(0%); 而在其非肠化腺体中，*H pylori* 阳性组PGC表达率低于阴性组(图2)，差异非常显著(P <0.01). 同时 *H pylori* 阳性组异型增生和胃癌PGC表达率也低于与其相应的阴性组，差异不显著(P >0.05，表1).

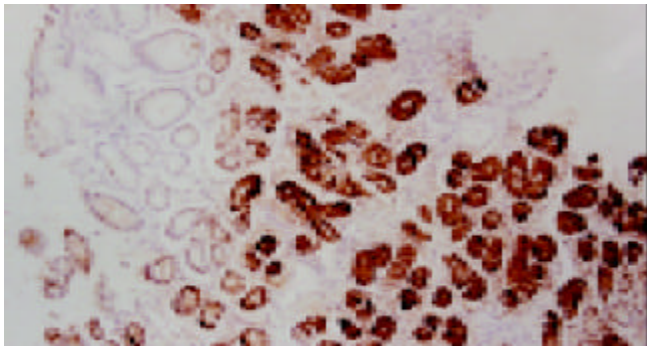

图1 *H pylori* 阳性浅表性胃炎PGC阳性表达(SP × 100).

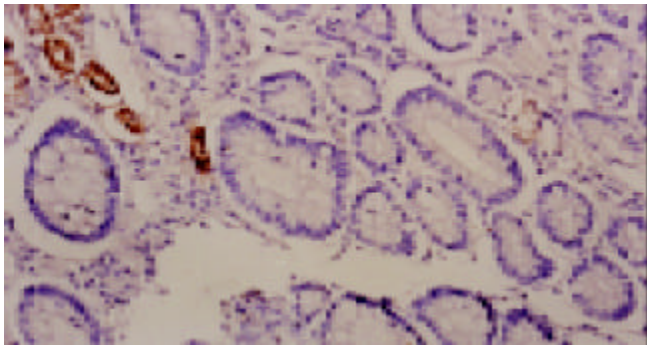

图2 *H pylori* 阳性萎缩性胃炎PGC阴性表达(SP × 200).

表1 PGC在 *H pylori* 相关性胃黏膜病变组织的表达

疾病分组		*H pylori* 阳性				*H pylori* 阴性				
	n	PGC阳性表达		PGC过表达		n	PGC阳性表达		PGC过表达	
		n	率(%)	n	率(%)		n	率(%)	n	率(%)
浅表性胃炎	33	33	100.0	28	84.8[a]	25	25	100.0	15	60.0
萎缩性胃炎	61	4	6.6[b]	0	0.0	30	9	30.0	1	3.3
肠上皮化生	61	0	0.0	0	0.0	30	0	0.0	0	0.0
异型增生	40	4	10.0	0	2.5	19	6	31.6	0	0.0
胃癌	58	0	0.0	0	0.0	52	3	5.8	0	0.0

[a] P <0.05, χ^2 = 0.032 28/33 *vs* 15/25, [b] P <0.01, χ^2 =0.003 4/61 *vs* 9/30.

3 讨论

多数萎缩性胃炎都与 *H pylori* 感染有关,*H pylori* 阳性患者胃癌的发生率是 *H pylori* 阴性患者的2.8-6倍[8-10]. *H pylori* 感染导致慢性胃炎及消化性溃疡进一步发展为萎缩性胃炎、肠化、异型增生乃至癌变这一观点已被广泛认可. 大多数的研究认为 *H pylori* 感染对胃癌的致病作用主要发生在病变早期[11-12]，对其在萎缩性胃炎以后的作用尚不清楚. 胃蛋白酶原(PG)是胃蛋白酶的前体,可分为胃蛋白酶原A(PGA)和胃蛋白酶原C(PGC)[13-14]. 合成的PG大部分进入胃腔，仅1%左右进入血循环. PGC最初出现于胚胎后期，是胃黏膜细胞分化成熟的终末产物，是消化功能逐渐成熟一种标志[4-5]. 近年来的研究表明，PGC的变化可以反映胃黏膜病变及分化程度，与胃黏膜萎缩、肠上皮化生、异型增生有关，慢性萎缩性胃炎和胃癌患者血清PGA的浓度和PGA/PGC的比值下降[6-7, 15-16]. 那么，*H pylori* 感染以后PGC如何表达呢?

我们发现，浅表性胃炎PGC均为阳性表达，但 *H pylori* 阳性组PGC的过表达率高于 *H pylori* 阴性组，这与血清学的研究结果相一致[7, 17]. 文献报道，PGC的水平与 *H pylori* 的定植密度成正比[18]，*H pylori* 引起慢性胃炎及胃溃疡患者血清PG水平升高，尤其使PGC升高更加明显; 根除 *H pylori* 后血清PGC水平下降[19]. *H pylori* 引起胃黏膜分泌PGC增多可能由于[20-23]: 可诱导PG基因的表达，脂多糖可刺激主细胞分泌胃蛋白酶原; 引起胃黏膜炎症，参与炎症反应多种细胞因子如白三烯、TNFα 可刺激主细胞分泌PGC; 可引起胃酸和胃泌素分泌增加，二者均能刺激PG分泌; 减少D细胞数量，抑制生长抑素分泌，减弱其对胃酸及胃蛋白酶原分泌的反馈性抑制，从而增加PG水平. 受损的胃黏膜血管通透性增加，血清PG水平增加. 大量PG进入胃腔，

遇酸活化形成胃蛋白酶，对黏膜造成溶解和破坏，促进胃黏膜炎症和溃疡形成.

*H pylori*感染的重度胃黏膜病变中PGC表达减少，肠化生黏膜PGC均为阴性表达，表明肠化上皮不合成PGC. *H pylori*阳性组的萎缩性胃炎PGC表达率低于*H pylori*阴性组(P <0.01); 在异型增生和胃癌中，也具有相同的趋势; PGC阳性的3例胃癌均为*H pylori*阴性，且均为高分化腺癌. 免疫组化研究表明[24-26]，PGC在萎缩性胃炎和胃癌组织中的表达显著下降，PGC的表达下降与胃癌细胞的去分化程度和疾病预后密切相关. 张祥宏 *et al* [27]通过对人群的随访研究发现，血清PG异常伴有*H pylori*感染者腺体萎缩、异型增生的发生率高于*H pylori*阴性者. *H pylori*感染的胃癌前疾病和胃癌黏膜PGC表达降低，可能由于*H pylori*引起的胃黏膜免疫-炎症反应和*H pylori*细胞毒性因子等共同作用，使自由基、超氧化物生成增加，这些致癌因子使胚细胞中的胃蛋白酶原基因受损突变，导致胃黏膜细胞的终末分化产物PGC-Ag表达减少，细胞分化程度降低，细胞增生、分化和凋亡失衡，癌变危险性增加.

总之，*H pylori*感染使胃黏膜炎症PGC表达增加，而在萎缩性胃炎、异型增生和胃癌阶段PGC的表达降低，对后者应密切随访，有利于提高胃癌早诊率、监测复发及预后.

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