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胃癌组织三叶肽因子2表达与幽门螺杆菌感染的相关性

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TFF2 expression and *H.pylori* infection in gastric cancer tissues

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Abstract

AIM:To investigate the relationship between the expression of TFF2 and *H.pylori* infection in human gastric precancerous lesions and gastric cancer, and to explore the role of TFF2 and *H.pylori* in human gastric precancerous lesions and gastric cancer.

METHODS:The expression of TFF2 was immunohistochemically analyzed in paraffin-embedded samples obtained by endoscopic biopsy and subtotal gastractomy specimens from 119 patients including chronic superficial gastritis (CSG, 16), chronic atrophic gastritis (CAG, 16), intestinal metaplasia (IM, 35), gastric epithelial dysplasia (GED, 23) and gastric cancer (CA, 25), and conditions of *H.pylori* infection were detected by means of Warthin-Starry staining.

RESULTS:TFF2 was located in the cell plasma of gastric mucous neck cells. The expressions of TFF2 were 100 %, 100 %, 0%, 56 % and 0% in CSG, CAG, IM, GED and CA, respectively. The density of TFF2 positive cells was higher in CSG with *H.pylori* infection than that without *H. pylori* infection (52.9±7.3 *vs* 46.5±13.0, P >0.05); but it was significantly lower in CAG and GED with *H. pylori* infection than that without *H. pylori* infection (18.2±4.1 *vs* 37.9±13.8, P <0.01 and 14.4±9.3 *vs* 24.8±10.2, P <0.05).

CONCLUSION:The high expression of TFF2 is associated with the protective mechanism after the gastric mucosal injury, the low expression of TFF2 in CAG might attribute to the decreased number of gastric gland cells secreting TFF2; but the re-expression of TFF2 in GED suggests that TFF2 is involved with the initiation of gastric cancer. The effect of *H. pylori* on the expression of TFF2 depends on the status of gastric mucosa.

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摘要

目的:观察三叶肽因子2(trefoil peptide 2, TFF2)在胃癌及癌前病变中的表达状况及其与 Hp 感染的关系，初步探讨 TFF2 与 Hp 感染在胃癌及癌前病变中的作用及意义.

方法:应用免疫组化方法测定16例慢性浅表性胃炎,20例慢性萎缩性胃炎，35 例肠上皮化生，23 例胃上皮不典型增生和 25 例胃癌中 TFF2 的蛋白表达情况，同时应用 Warthin-Starry 法检测幽门 Hp 情况.

结果:(1)在慢性浅表性胃炎,慢性萎缩性胃炎，胃上皮不典型增生中均有 TFF2 的阳性表达,其阳性率分别为 100 %，100 %和 56.5 %.而在肠上皮化生和胃癌组织内无 TFF2 的阳性表达，但在肠上皮化生周围的正常腺体有 TFF2 阳性表达.慢性浅表性胃炎TFF2的染色评分明显高于慢性萎缩性胃炎组.(2)在浅表性胃炎中,Hp 感染阳性病例 TFF2 的阳性细胞密度值高于 Hp 感染阴性者(52.9 ± 7.3 vs 46.5 ± 13.0),但无统计学意义(P >0.05).而在胃黏膜萎缩及胃黏膜上皮不典型增生中，Hp 感染者 TFF2 的阳性细胞密度值又低于 Hp 感染阴性者,差异有显著性(18.2 ± 4.1vs 37.9 ± 13.8, P <0.01 和 14.4 ± 9.3 vs 24.8 ± 10.2, P <0.05).

结论: TFF2在慢性浅表性胃炎中的高表达与黏膜损伤后所诱导的保护机制有关；慢性萎缩性胃炎 TFF2 的表达相对减少可能与分泌 TFF2 的胃黏膜腺体减少有关；但在不典型增生中 TFF2 的再表达可能参与了胃癌发生的早期阶段；Hp感染对TFF2表达的影响可能取决于胃黏膜病变的状态.

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0 引言

三叶肽因子 2(trefoil factor family 2, TFF2)，又名解痉多肽(spasmolytic polypeptide, SP),是三叶肽家族成员之一.正常情况下，胃 TFF2 主要由的胃体和胃窦的胃腺上皮黏液颈细胞合成与分泌[1,2].当胃肠道在不同的病理条件下时，TFF2 基因表达迅速被上调，参与胃肠道

上皮的重建和修复过程.在Hp感染的慢性胃黏膜病变演化过程中，黏膜的损伤与修复是一持续存在的过程.TFF2作为一种黏膜保护因子，可能在此过程中发挥了一定的作用.目前关于TFF2在胃癌及癌前病变中的表达情况的研究较少，与Hp感染的关系尚不清楚，我们通过免疫组织化学和Warthin-Starry染色法系统地回顾性检测胃癌及癌前病变中TFF2的蛋白表达和Hp感染情况，并探讨二者的相互关系，进一步阐明TFF2与Hp感染在胃癌及癌前病变中的作用及意义.

1 材料和方法

1.1材料 武汉大学人民医院2000-03/2001-03期间存档的胃镜活检及手术切除后标本119例.其中浅表行胃炎16例，萎缩性胃炎20例，胃黏膜肠上皮化生31例，胃上皮不典型增生20例及胃癌(均含癌旁黏膜)25例.男72例,女40例,中位数为35岁.所有标本均用40 g/L甲醛固定，常规脱水，透明，浸蜡，制成4 μm厚连续切片.鼠抗人TFF2单克隆抗体原液(novocastra Ltd)，以1∶35稀释后待用；S-P试剂盒购自福州迈新公司；DAB购自Dako公司；

1.2 方法 石蜡切片染色前常规脱蜡至水,微波炉抗原修复20 min,染色采用SP法，DAB显色，具体操作过程按SP试剂盒说明书完成.并设立阳性对照和阴性对照(以TBS缓冲液代替一抗).免疫组化完成后24 h内光镜下阅片，TFF2染色评分标准：每张切片随机选取5个100× 视野，阳性细胞数<5 % 为(-)，5-25 % 为(+)，25-75 % 为(++),>75 % 为(+++).同时采用全自动彩色图像分析仪，HPIAS2000型图像分析软件检测阳性细胞密度值，用此间接反映TFF2蛋白的表达量.组织片常规脱蜡至水，0.2 mol/L醋酸缓冲液洗2次,入10 g/L硝酸银液内约1 h，立即浸入显影液内2-3 min，56 ℃蒸馏水洗1-2 min，蒸馏水洗1次，依次脱水，透明，中性树胶封片，油镜下观察.见到胃黏膜表面和（/或）胃小凹及肿瘤性腺腔中，棕褐色弯曲棒状或圆颗粒状小体，则为Hp感染阳性，无Hp检出者为Hp感染阴性.

统计学处理 以上数据均采用SPSS10.0统计分析软件进行t检验分析，以P <0.05为有统计学意义.

2 结果

2.1 TFF2在胃黏膜病变演化中的表达 TFF2阳性表达于胃黏膜上皮近基底部的胃腺上皮的细胞质内，呈棕褐色，在慢性浅表性胃炎,慢性萎缩性胃炎，胃上皮不典型增生中均有TFF2的阳性表达，其阳性率分别为100 %，100 % 和56.5 %(见图1-3).而在肠上皮化生和胃癌组织内无TFF2的阳性表达，在肠上皮化生周围的正常腺体有TFF2阳性表达(见图4,5).慢性浅表性胃炎TFF2的染色评分高于慢性萎缩性胃炎组(见表1).

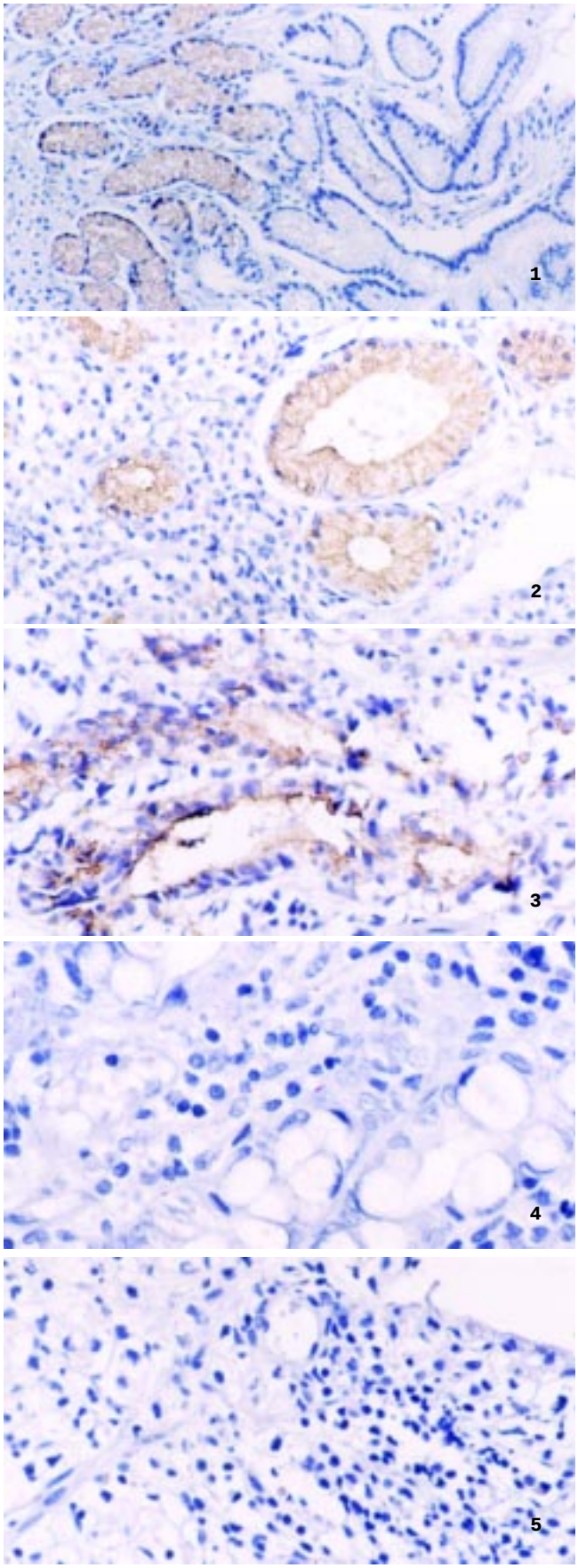

图1 TFF2在慢性浅表性胃炎中的表达 阳性染色于细胞质(SP×100)
图2 TFF2在慢性萎缩性胃炎中的表达 阳性染色于细胞质(SP×200)
图3 TFF2在胃上皮不典型增生中的表达 阳性染色于细胞质(SP×200)
图4 TFF2在肠上皮化生中无表达 在周围正常腺体中有表达(SP×400)
图5 TFF2在胃癌中的无表达(SP×200)

表 1 TFF2 在不同胃黏膜病变中的表达模式

分类	*n*	TFF2				阳性率%
		−	+	++	+++	
浅表性胃炎	16	0	1	5	10	100
萎缩性胃炎	20	0	5	11	4	100
肠上皮化生	35	35	0	0	0	0
不典型增生	23	10	9	2	2	56.5
胃腺癌	25	25	0	0	0	0

2.2 TFF2 的表达与 Hp 感染的关系 本组胃黏膜 Hp 的总检出率为 53.8 %,浅表性胃炎为 50 %,萎缩性胃炎为 60.0 %,胃黏膜肠上皮化生为45.7 %,胃黏膜不典型增生为 52.5 %,胃癌为 64 %.在浅表性胃炎中，Hp 感染阳性病例 TFF2 的阳性细胞密度值高于 Hp 感染阴性者，但无统计学意义(52.9 ± 7.3 vs 46.5 ± 13.0, P >0.05)(考虑原因: (1)病历数少；(2)肉眼观察 Hp 染色可能存在偏差).而在胃黏膜萎缩及胃黏膜上皮不典型增生中，Hp 感染者 TFF2 的阳性细胞密度值又低于 Hp 感染阴性者,差异有显著性,(18.2 ± 4.1 vs 37.9 ± 13.8, P <0.01 和 14.4 ± 9.3 vs 24.8 ± 10.2, P <0.05).

3 讨论

大量研究表明[3-7]，TFF2 可能通过增强受损黏膜周围完好的上皮细胞向黏膜损伤表面迁移覆盖，阻止质子对黏液层的渗透，或与黏液中的糖蛋白相互作用，加强黏液凝胶层抵抗黏膜表面有害物质的损伤等多种途径来保护胃黏膜.我们发现，TFF2在所有的慢性浅表性胃炎和萎缩性胃炎中均高表达，进一步说明了 TFF2 的表达是胃黏膜损伤所诱导的一种黏膜修复和保护机制.慢性萎缩性胃炎 TFF2 的染色评分低于慢性浅表性胃炎，可能与分泌 TFF2 的胃黏膜腺体的数量因萎缩减少有关.在肠上皮化生和胃癌组织内无 TFF2 的阳性表达，但在肠上皮化生周围和癌旁正常腺体却有TFF2阳性表达，提示 TFF2 的表达可能与胃腺上皮细胞的分化表型有关.Machado et al[8]研究发现，在 96 例胃癌中有 10 例表达TFF2(10.4 %),而本组25例胃癌中却未发现TFF2的表达,可能与我们收集的胃癌病例较少有关.我们发现，在不典型增生中 TFF2 又重新获得表达，而不典型增生正是胃癌的癌前病变形式，这似乎提示 TFF2 可能在胃癌的发生早期起一定作用.早在 1999 年,Schmidt et al[9]就发现,一种表达 TFF2 的化生细胞系 SPEM(SP-expressing metaplastic lineage)出现在 91 % 的胃腺癌中,且典型的 SPEM 细胞位于癌组织和不典型增生邻近的黏膜区域.随后,Yamaguchi et al[10]也发现SPEM细胞出现在残胃癌组织的周围黏膜和胃癌手术切除活检的标本中.以上均提示 SPEM 细胞与胃癌的发生有明显的相关性,但 TFF2 与胃癌的关系尚无定论.最近 Farrell et al[11]研究发现，在 TFF2 缺陷鼠模型实验中，实验鼠的胃黏膜增生减低，胃酸相应增加，暗示 TFF2 通过刺激黏膜增生和降低胃酸分泌起到提高黏膜修复的功能.但在另一方面，TFF2 的刺激黏膜增生和降低胃酸分泌的作用又将增加胃癌发生的风险.

胃癌是消化道最常见的恶性肿瘤之一[12-20],Hp 感染又是导致胃黏膜病变最常见的致病因子之一[21-40].TFF2 作为一种黏膜保护因子，是否 Hp 感染会影响 TFF2 的表达呢？已有研究报道[9,41,42]，在 Hp 感染的患者和伴有胃黏膜癌前和癌性病变的 Hp 感染小鼠中，都发现表达 TFF2 的胃黏液颈细胞的数量有增加，这似乎提示 Hp 感染可能引起胃黏液细胞的增生，从而增加 TFF2 的表达.为了进一步阐清 TFF2 在 Hp 感染性胃黏膜病变中的作用，我们又回顾性的检测了 Hp 的感染情况，发现在浅表性胃炎中,Hp 感染阳性病例 TFF2 的阳性细胞密度值高于 Hp 感染阴性者,虽无统计学意义(P >0.05),但提示 Hp 感染的早期是刺激或诱导 TFF2 表达的，可能与 Hp 感染刺激胃黏液细胞增生有关.而在胃黏膜萎缩及胃黏膜上皮不典型增生中，Hp 感染者 TFF2 的阳性细胞光密度值又低于 Hp 感染阴性者，我们推测可能是 Hp 感染所导致正常分泌 TFF2 的胃黏膜上皮细胞的大量破坏减少的结果.由上可见，Hp 感染影响 TFF2 表达的变化可能与胃黏膜状态有关，Hp 感染是否直接影响 TFF2 基因的表达，还须进一步的研究.

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