世界华人消化杂志®
wcjd@wjgnet.com
世界华人消化杂志 2006年3月8日; 14(7): 660-665
ISSN 1009-3079 CN 14-1260/R

基础研究 BASIC RESEARCH

胃癌组织Maspin, uPA, MMP-7表达的意义

邓 玮, 易永芬, 刘丹丹

■背景资料
Maspin是一种新发现的丝氨酸蛋白酶抑制剂, 已在多种肿瘤中证实其具有抑制肿瘤侵袭、转移的作用. 但有关Maspin在胃癌中的研究, 国内外报道很少. 我们对Maspin在胃癌组织的表达进行了研究, 探讨了其表达与临床病理的关系, 首次分析了胃癌组织Maspin, uPA, MMP-7表达的相关性及其意义, 初步探讨了Maspin可能的作用机制, 为以后更深入的研究打下基础.

邓玮, 易永芬, 刘丹丹, 重庆医科大学病理教研室 重庆市 400016
邓玮, 2003年重庆医科大学硕士生, 主要从事消化系统肿瘤的研究.
重庆市教委资助项目, No. 040310
通讯作者: 易永芬, 400016, 重庆市医学院路1号, 重庆医科大学病理科. yiyongfen1953@yahoo.com.cn
电话: 023-68485789
收稿日期: 2005-12-31 接受日期: 2006-01-26

Significance of Maspin, uPA and MMP-7 expression in human gastric carcinoma

Wei Deng, Yong-Fen Yi, Dan-Dan Liu

Wei Deng, Yong-Fen Yi, Dan-Dan Liu, Department of Pathology, Chongqing Medical University, Chongqing 400016, China
Supported by the Fund from Chongqing Education Committee, No. 040310
Correspondence to: Yong-Fen Yi, Department of Pathology, Chongqing Medical University, Chongqing 400016, China. Yiyongfen1953@yahoo.com.cn
Received: 2005-12-31 Accepted: 2006-01-26

Abstract

AIM: To investigate the expression of Maspin, urokinase-type plasrninogen activator (uPA) uPA and Matrix metalloproteinase-7 (MMP-7) and their roles in the tumorigenesis and progression of gastric cancer.

METHODS: Immunohistochemistry SP method was used to detect the expression of Maspin, uPA and MMP-7 in tissues from gastric adenocarcinoma (n = 30), signet-ring cell carcinoma (n = 30), and normal gastric mucosa (n = 20).

RESULTS: The positive rates of Maspin, uPA and MMP-7 were 50%, 70% and 80%, respectively, in gastric adenocarcinoma, and they were 46.7%, 76.7% and 90%, respectively, in signet-ring cell carcinoma. However, the positive rates of Maspin, uPA, and MMP-7 were 90%, 35%, and 30%, respectively, in normal gastric mucosa. Maspin, uPA, and MMP-7 expression were significantly different between tissues from carcinoma and normal mucosa ($P < 0.05$ or $P < 0.01$). Maspin expression was significantly related to the depth of invasion and lymph node metastasis, but not to tumor size and TNM staging. The expression of uPA and MMP-7 were markedly related to the depth of invasion, lymph node metastasis and TNM staging, but not to tumor size. Maspin expression had a negative correlation with uPA and MMP-7 (P = 0.012, r = -0.322; P = 0.008, r = -0.341), while uPA expression had a positive correlation with MMP-7 (P = 0.034, r = 0.274).

CONCLUSION: Down-regulated expression of Maspin and up-regulated expression of uPA and MMP-7 play important roles in the invasion and metastasis of gastric carcinoma. They may serve as effective markers of reflecting the biopathological behaviors of gastric carcinoma.

Key Words: Gastric tumor; Maspin; Urokinase-type plasrninogen activator; Matrix metalloproteinase-7

Deng W, Yi YF, Liu DD. Significance of Maspin, uPA and MMP-7 expression in human gastric carcinoma. Shijie Huaren Xiaohua Zazhi 2006;14(7):660-665

摘要

目的: 观察胃癌及正常胃黏膜Maspin, uPA, MMP-7表达的意义.

方法: 应用免疫组化SP法检测胃管状腺癌30例, 胃印戒细胞癌30例, 正常胃黏膜组织20例中Maspin, uPA, MMP-7的表达情况.

结果: 在胃管状腺癌中Maspin, uPA, MMP-7阳性表达率分别为50%, 70%和80%; 胃印戒细胞癌中阳性表达率分别为46.7%, 76.7%和90%; 正常胃黏膜组织中阳性表达率分别为90%, 35%和30%. Maspin的表达与浸润深度、淋巴结转移相关, 而与肿块的大小和TNM分期无关. uPA和MMP-7的表达与浸润深度、淋巴结转移、TNM分期相关, 而与肿块的大小无关. Maspin的表达与uPA和MMP-7的表达呈负相关(P = 0.012, r = -0.322; P = 0.008, r = -0.341); uPA的表达与MMP-7的表达呈正相关(P = 0.034, r = 0.274).

结论: Maspin在胃癌中表达下调, uPA和MMP-7在胃癌中过表达, 他们在胃癌的浸润转移中起重要作用, 可作为反应胃癌病理生物学行为的有效指标.

关键词: 胃癌; Maspin; 尿激酶型纤溶酶原激活物; 基质金属蛋白酶-7

邓玮, 易永芬, 刘丹丹. 胃癌组织Maspin, uPA, MMP-7表达的意义. 世界华人消化杂志 2006;14(7):660-665
http://www.wjgnet.com/1009-3079/14/660.asp

■创新盘点
我们对Maspin在胃癌组织的表达进行了研究, 探讨了其表达与临床病理的关系, 首次分析了胃癌组织Maspin, uPA, MMP-7表达的相关性及其意义, 初步探讨了Maspin可能的作用机制, 为以后更深入的研究打下基础.

0 引言

胃癌是常见的消化系统恶性肿瘤之一, 许多基因在胃癌的浸润转移中发挥重要作用. Maspin基因是丝氨酸蛋白酶抑制剂超家族中的一种, 分子质量为42 ku, 具有肿瘤抑制活性. 大量研究表明, 在多种肿瘤比如乳腺癌、口腔鳞癌中, Maspin的表达与其预后有关. 而Maspin基因的缺失会导致肿瘤浸润转移能力的增强. MMP-7和uPA分别属于金属蛋白酶类和丝氨酸蛋白酶类, 他们能有效地降解细胞外基质, 与恶性肿瘤发生和发展密切相关. 但是, 联合检测Maspin, uPA, MMP-7与胃癌的生物学特性的关系尚未见报道. 我们应用免疫组化SP染色法, 检测Maspin, uPA, MMP-7在胃管状腺癌、胃印戒细胞癌及正常胃黏膜组织中的表达, 并探讨他们之间的关系及其在胃癌浸润转移中的作用.

1 材料和方法

1.1 材料 1998-01/2004-01手术切除(术前未化疗)的胃癌组织石蜡块80例, 其中胃管状腺癌30例, 印戒细胞癌30例. 正常胃黏膜组织20例取自胃癌手术切除标本的正常切缘, 切缘经组织学证实无癌组织浸润. 胃癌中肿块≥4 cm 36例, <4 cm 24例. 侵及黏膜及黏膜下层者8例, 侵及固有肌层者13例, 侵及浆膜层者39例. 有局部淋巴结转移者36例, 无淋巴结转移者24例. TNM 0, Ⅰ期24例; Ⅱ, Ⅲ, Ⅳ期36例. Maspin即用型mAb(MS-1767-R7)购自美国Neomaker公司, uPA mAb购自武汉博士德公司, MMP-7 mAb购自福州迈新公司, SP-9000购自北京中杉生物公司.

1.2 方法 采用免疫组化SP法, 切片常规脱蜡至水, 30 mL/L过氧化氢孵育10 min, pH 8.0的EDTA缓冲液微波修复5 min, 滴加正常山羊血清工作液孵育10 min, 一抗4℃过夜, 滴加二抗, 孵育15 min, 滴加三抗, 孵育15 min, DAB显色, 苏木素复染, 脱水, 透明, 封片. PBS代替一抗作阴性对照, 已知阳性切片作阳性对照. Maspin定位于细胞质内或细胞质细胞核同时着色. 依据染色强度及阳性细胞率来计算评分. 染色强度: 0为阴性, 1为弱阳性, 2为阳性, 3为强阳性; 阳性细胞数0, <1%, <10%, <1/3, <2/3, >2/3分别积分为0, 1, 2, 3, 4, 5; 两项之和0-2分为阴性(-), 3-5分为阳性(+), 6-8分为强阳性(++). uPA定位于细胞质内, 细胞质呈棕黄色者为阳性细胞, 依据染色强度及阳性细胞率来计算评分. 染色强度: 0为阴性, 1为弱阳性, 2为阳性, 3为强阳性; 阳性细胞数0, 1%-25%, 25%-50%, >50%分别积分为0, 1, 2, 3; 两项之和为3-6分者评为免疫组织化学染色阳性. MMP-7定位于细胞质内, 取10个高倍视野1 000个细胞计数阳性细胞数, 阳性细胞<10%为阴性, ≥10%为阳性.

统计学处理 应用SPSS 11.5统计软件进行统计分析. 采用χ^2检验及Spearman等级相关分析. 检验水准为0.05.

2 结果

2.1 Maspin, uPA, MMP-7的表达 Maspin主要表达于正常胃黏膜的腺上皮细胞和胃癌细胞的细胞质(图1). 在胃管状腺癌中Maspin阳性表达率为50%(15/30), 9例为阳性(+), 6例为强阳性(++), 强阳性率为20%; 胃印戒细胞癌中Maspin阳性表达率为46.7%(14/30), 10例为阳性(+), 4例为强阳性(++), 强阳性率为13.3%; 正常胃黏膜组织中Maspin阳性表达率为90%(18/20), 5例为阳性(+), 13例为强阳性(++), 强阳性率为65%. 正常胃黏膜组织中Maspin阳性表达率和阳性表达强度明显高于胃管状腺癌和胃印戒细胞癌(P<0.05), 而胃管状腺癌和胃印戒细胞癌之间Maspin阳性表达率无明显差别(P>0.05). uPA阳性物质主要位于正常胃黏膜的腺上皮细胞和肿瘤细胞的胞质(图2), 30例胃管状腺癌中uPA阳性表达率为70%(21/30), 30例胃印戒细胞癌中uPA阳性表达率为76.7%(23/30), 20例正常胃黏膜组织中uPA阳性表达率为35%(7/20). 正常胃黏膜组织中uPA阳性表达率明显低于胃管状腺癌和胃印戒细胞癌(P<0.05), 而胃管状腺癌和胃印戒细胞癌之间无明显差别(P>0.05). 正常胃黏膜和肿瘤细胞MMP-7阳性者为胞质中出现棕黄色颗粒(图3). 30例胃管状腺癌中MMP-7阳性表达率为80%(24/30), 30例胃印戒细胞癌中阳性表达率90%(27/30), 20例正常胃黏膜组织中阳性表达率为30%(6/20). 正常胃黏膜组织中MMP-7阳性表达率明显低于胃管状腺癌和胃印戒细胞癌

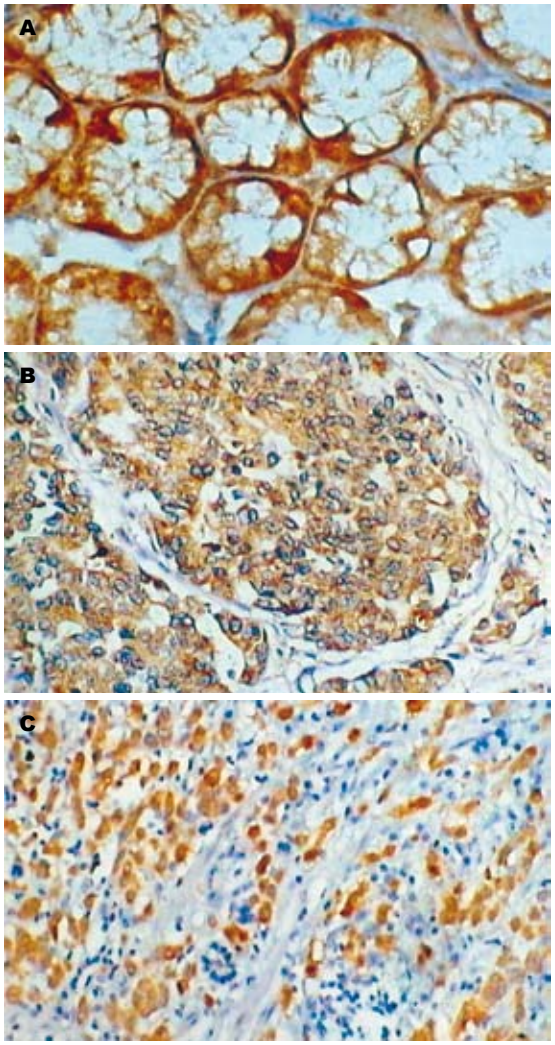

图 1 胃黏膜Maspin阳性表达. A: 正常; B: 胃管状腺癌; C: 胃印戒细胞癌.

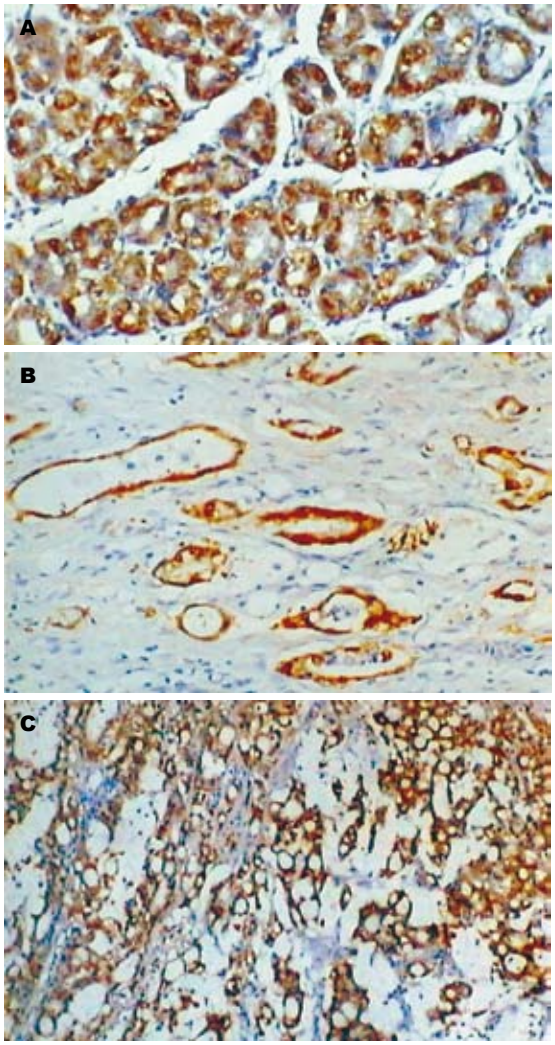

图 2 胃黏膜uPA阳性表达. A: 正常; B: 胃管状腺癌; C: 胃印戒细胞癌.

表 1 胃癌组织Maspin, uPA, MMP-7 +, ++ (%) 的表达

分组	*n*	Maspin		uPA		MMP-7	
		+ ~ ++	(%)	+ ~ ++	(%)	+ ~ ++	(%)
胃管状腺癌	30	9	6 (50.0)[b]	21	(70.0)[a]	24	(80.0)[b]
胃印戒细胞癌	30	10	4 (46.7)[b]	23	(76.7)[b]	27	(90.0)[b]
正常胃黏膜	20	5	13 (90.0)	7	(35.0)	6	(30.0)

[a]$P<0.05$, [b]$P<0.01$ *vs* 正常胃黏膜.

($P<0.05$), 而胃管状腺癌和胃印戒细胞癌之间无明显差别($P>0.05$, 表1).

2.2 Maspin, uPA, MMP-7与胃癌临床病理特征的关系 肿瘤的大小和TNM分期与Maspin的阳性表达率无明显关系($P>0.05$). 而浸润深度与Maspin的阳性表达率有相关性, 侵及黏膜及黏膜下、侵及肌层和侵及浆膜层者阳性率分别为75%(6/8), 61.5%(8/13), 38.5%(15/39), 有统计学意义($P<0.05$). 无淋巴结转移者Maspin的阳性表达率为66.6%(16/24), 有淋巴结转移者为36.1%(13/36), 前者明显高于后者($P<0.05$). 肿瘤的大小与uPA和MMP-7的阳性表达率无明显关系($P>0.05$). 60例胃癌组织中uPA的阳性表达与浸润深度有关, 侵及黏膜及黏膜下、侵及肌层和侵及浆膜层者阳性率分别为50%(4/8), 61.5%(8/13), 82.1%(32/39), 有统计学意义($P<0.05$); 无淋巴结转移者阳性表达率为54.2%(13/24), 有淋巴结转移者阳性表达率86.1%(31/36), 差异有显著性; TNM分期中0, Ⅰ期和Ⅱ, Ⅲ, Ⅳ期胃癌组织阳性表达率分别为58.3%(14/24), 83.3%(30/36), 有统计学意义($P<0.05$). 胃癌组织中MMP-7的阳性表达与浸润深度有关, 侵及黏膜及黏膜下、侵及肌层和侵及浆膜层者阳性率分别为62.5%(5/8), 76.9%(10/13), 92.3%(36/39), 有统

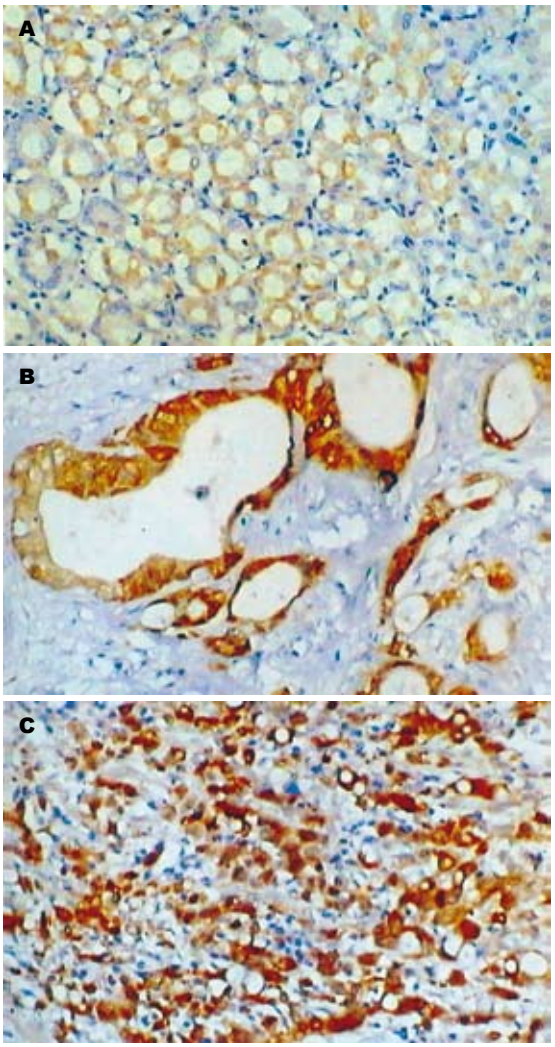

图 3 胃黏膜MMP-7阳性表达. A: 正常; B: 胃管状腺癌; C: 胃印戒细胞癌.

计学意义(P<0.05); 无淋巴结转移者阳性表达率为70.8%(17/24), 有淋巴结转移者阳性表达率94.4%(34/36), 二者有显著差异; TNM分期中0, Ⅰ期和Ⅱ, Ⅲ, Ⅳ期胃癌组织阳性表达率分别为70.8%(17/24), 94.4%(34/36), 二者有显著差异(表2).

2.3 胃癌Maspin, uPA, MMP-7表达的相关性 胃癌组织中17例Maspin与uPA同时阳性表达, 4例Maspin与uPA同时阴性表达, Maspin与uPA表达呈负相关(P<0.05). 21例Maspin与MMP-7同时阳性表达, 1例同时阴性表达, Maspin与MMP-7表达呈负相关(P<0.05). 40例uPA与MMP-7同时阳性表达, 9例uPA与MMP-7同时阴性表达, uPA与MMP-7表达呈正相关(P<0.05, 表3).

3 讨论

Maspin是丝氨酸蛋白酶抑制剂超家族中的一种, 具有抑制肿瘤的活性. 目前研究表明Maspin在多种正常细胞如乳腺、阴道、前列腺、皮肤的上皮细胞中高表达[1-2], 而在癌细胞如口腔鳞癌、乳腺癌中表达下调或缺失[3-6]. 我们的研究也显示正常胃黏膜中Maspin的阳性表达率明显高于胃管状腺癌和胃印戒细胞癌, 而胃管状腺癌和胃印戒细胞癌之间的阳性表达率无显著差异. 此结果提示Maspin表达下调与胃癌的恶性演进有关. 有作者报道癌细胞中Maspin的启动子出现cytosine甲基化, 而用甲基化抑制剂后, Maspin重新表达, 且出现剂量依赖, 这提示Maspin基因表达的下调与甲基化有关[7-9]. 也有作者认为Maspin表达下调与转录因子Ets和Ap1的转录活性失活有关, 正常上皮细胞中Ets可和Ap1协同作用, 激活启动子转录, 而癌细胞中Ets和Ap1正调节作用减弱, Maspin表达降低[10]. 我们讨论了Maspin的表达与临床病理特征的关系, 发现Maspin的表达与浸润和转移有关. 即浸润越深、有转移者Maspin表达越低. 这提示Maspin作为肿瘤转移抑制基因在胃癌演进中起着重要的抑制作用, 这与Maspin在其他肿瘤演进中

表 2 胃癌组织Maspin, uPA, MMP-7表达与临床病理特征的关系

临床病理	n	Maspin	uPA	MMP-7
肿块大小				
<4 cm	24	13	18	20
≥4 cm	36	16	26	31
浸润深度				
达黏膜及黏膜下	8	5	4	5
达固有肌层	13	9[a]	8[a]	10
达浆膜层	39	15	32	36
淋巴结转移				
无	24	16	13	17
有	36	13[a]	31[b]	34[a]
TNM分期				
0, Ⅰ期	24	13	14	17
Ⅱ, Ⅲ, Ⅳ	36	16	30[a]	34[a]

[a]P<0.05, [b]P<0.01.

表 3 胃癌组织Maspin, uPA, MMP-7表达的关系

项目		Maspin		r_s	P值	uPA		r_s	P值
		−	+			−	+		
MMP-7	−	1	8			9	0		
	+	30	21	−0.341	0.008	11	40	0.274	0.034
uPA	−	4	12						
	+	27	17	−0.322	0.012				

的表现是吻合的[11-15]. 大量研究表明, Maspin在肿瘤浸润转移的各个环节中起着重要的作用: Maspin能改变细胞表面整合素的结构, 增强细胞对细胞外基质的黏附能力, 影响细胞内的信号传导, 使细胞向更良性表型转化[16]; Maspin能有效阻止内皮细胞对血管生长因子的反应, 抑制内皮细胞的生长, 阻止其形成管道结构, 使肿瘤微血管的密度减少[17-19]. 最近的研究表明Maspin还可以通过调节小G蛋白Rac1和PAK1(p21-活性激酶)的活性来抑制细胞的运动, 通过磷酰肌醇-3激酶(PI3K)和细胞外信号调节激酶(ERK)途径来调节细胞的黏附[20].

uPA是一种丝氨酸蛋白酶, 与特异性受体(uPAR)结合后, 具有活性, 能启动纤溶酶原活化为纤溶酶, 后者能降解肿瘤细胞外基质, 促进肿瘤的浸润转移. 我们发现, 正常胃黏膜中uPA的阳性表达率明显低于胃管状腺癌和胃印戒细胞癌, 且胃癌中浸润越深、有转移者uPA阳性表达越高. 这与Okusa *et al*[21]发现uPA高活性与肿瘤浸润深度和转移相关是一致的. 我们还发现Maspin的表达与uPA呈负相关, Biliran *et al*[22]发现Maspin可特异抑制细胞表面相关的uPA, 从而降低体外细胞的浸润运动潜能. 且有作者发现重组Maspin的反应活性部位是RSL结构, 能特异地与单链纤维蛋白溶酶原激活物结合, 形成稳定的复合物, 从而抑制纤维蛋白溶酶原激活物的活性[23-25]. 此外, Maspin可与uPA结合形成一种抗SDS的蛋白酶复合物, 降低uPA的释放能力, 减少纤溶酶原活化为纤溶酶.

MMP-7是MMP家族的重要成员, 他能降解基底膜成分如Ⅳ型胶原和弹性蛋白. 有作者发现胃癌中MMP-7表达增强[26-28]. 本研究发现正常胃黏膜中MMP-7的阳性表达率明显低于胃腺癌和胃印戒细胞癌, 且胃癌中浸润越深、有转移者MMP-7阳性表达越高. 这与其他作者的发现是一致的. 此外, uPA与MMP-7表达呈正相关. 有研究表明: uPA可以激活MMP, 开启MMP对细胞外基质的降解机制, 主要是uPA通过细胞外信号通路酪氨酸激酶活性包括Src和磷酰肌醇-3激酶(PI3K), 与整合素β1结合, 激活pro-MMP, 从而调节MMP的活性[29-30]. Maspin与MMP-7表达呈负相关, 这提示Maspin对MMP-7可能有下调作用, 我们推测其机制可能是Maspin通过下调uPA的表达, 从而影响信号传导系统使MMP-7的表达下降, 但其具体作用机制有待进一步探讨.

总之, 我们的结果提示, Maspin表达的下调和uPA, MMP-7的过表达在胃癌的浸润转移中起重要作用, 他们可以作为反映胃癌病理生物学行为的指标. 但三者之间是如何调节的有待进一步研究.

4 参考文献

1 Cao D, Wilentz RE, Abbruzzese JL, Ho L, Maitra A. Aberrant expression of Maspin in idiopathic inflammatory bowel disease is associated with disease activity and neoplastic transformation. *Int J Gastrointest Cancer* 2005; 36: 39-46

2 Marioni G, Blandamura S, Giacomelli L, Calgaro N, Segato P, Leo G, Fischetto D, Staffieri A, de Filippis C. Nuclear expression of Maspin is associated with a lower recurrence rate and a longer disease-free interval after surgery for squamous cell carcinoma of the larynx. *Histopathology* 2005; 46: 576-582

3 Xia W, Lau YK, Hu MC, Li L, Johnston DA, Sheng S, El-Naggar A, Hung MC. High tumoral Maspin expression is associated with improved survival of patients with oral squamous cell carcinoma. *Oncogene* 2000; 19: 2398-2403

4 Umekita Y, Yoshida H. Expression of Maspin is up-regulated during the progression of mammary ductal carcinoma. *Histopathology* 2003; 42: 541-545

5 Friedrich MG, Toma MI, Petri S, Cheng JC, Hammerer P, Erbersdobler A, Huland H. Expression of Maspin in non-muscle invasive bladder carcinoma: correlation with tumor angiogenesis and prognosis. *Eur Urol* 2004; 45: 737-743

6 Chen Z, Fan Z, McNeal JE, Nolley R, Caldwell MC, Mahadevappa M, Zhang Z, Warrington JA, Stamey TA. Hepsin and Maspin are inversely expressed in laser capture microdissectioned prostate cancer. *J Urol* 2003; 169: 1316-1319

7 Futscher BW, Oshiro MM, Wozniak RJ, Holtan N, Hanigan CL, Duan H, Domann FE. Role for DNA methylation in the control of cell type specific Maspin expression. *Nat Genet* 2002; 31: 175-179

8 Ito R, Nakayama H, Yoshida K, Oda N, Yasui W. Loss of Maspin expression is associated with development and progression of gastric carcinoma with p53 abnormality. *Oncol Rep* 2004; 12: 985-990

9 Primeau M, Gagnon J, Momparler RL. Synergistic antineoplastic action of DNA methylation inhibitor 5-AZA-2'-deoxycytidine and histone deacetylase inhibitor depsipeptide on human breast carcinoma cells. *Int J Cancer* 2003; 103: 177-184

10 Zhang M, Magit D, Sager R. Expression of Maspin in prostate cells is regulated by a positive ets element and a negative hormonal responsive element site recognized by androgen receptor. *Proc Natl Acad Sci USA* 1997; 94: 5673-5678

11 Machtens S, Serth J, Bokemeyer C, Bathke W, Minssen A, Kollmannsberger C, Hartmann J, Knuchel R, Kondo M, Jonas U, Kuczyk M. Expression of the p53 and Maspin protein in primary prostate cancer: correlation with clinical features. *Int J Cancer* 2001; 95: 337-342

12 Yasumatsu R, Nakashima T, Hirakawa N, Kumamoto Y, Kuratomi Y, Tomita K, Komiyama S. Maspin expression in stage I and II oral tongue squamous cell carcinoma. *Head Neck* 2001; 23: 962-966

13 Maass N, Hojo T, Rosel F, Ikeda T, Jonat W, Nagasa-

ki K. Down regulation of the tumor suppressor gene Maspin in breast carcinoma is associated with a higher risk of distant metastasis. *Clin Biochem* 2001; 34: 303-307
14 Reddy KB, McGowen R, Schuger L, Visscher D, Sheng S. Maspin expression inversely correlates with breast tumor progression in MMTV/TGF-alpha transgenic mouse model. *Oncogene* 2001; 20: 6538-6543
15 Domann FE, Rice JC, Hendrix MJ, Futscher BW. Epigenetic silencing of Maspin gene expression in human breast cancers. *Int J Cancer* 2000; 85: 805-810
16 Seftor RE, Seftor EA, Sheng S, Pemberton PA, Sager R, Hendrix MJ. Maspin suppresses the invasive phenotype of human breast carcinoma. *Cancer Res* 1998; 58: 5681-5685
17 Zhang M, Volpert O, Shi YH, Bouck N. Maspin is an angiogenesis inhibitor. *Nat Med* 2000; 6: 196-199
18 Shi HY, Zhang W, Liang R, Abraham S, Kittrell FS, Medina D, Zhang M. Blocking tumor growth, invasion, and metastasis by Maspin in a syngeneic breast cancer model. *Cancer Res* 2001; 61: 6945-6951
19 Wang MC, Yang YM, Li XH, Dong F, Li Y. Maspin expression and its clinicopathological significance in tumorigenesis and progression of gastric cancer. *World J Gastroenterol* 2004; 10: 634-637
20 Odero-Marah VA, Khalkhali-Ellis Z, Chunthapong J, Amir S, Seftor RE, Seftor EA, Hendrix MJ. Maspin regulates different signaling pathways for motility and adhesion in aggressive breast cancer cells. *Cancer Biol Ther* 2003; 2: 398-403
21 Okusa Y, Ichikura T, Mochizuki H. Prognostic impact of stromal cell-derived urokinase-type plasminogen activator in gastric carcinoma. *Cancer* 1999; 85: 1033-1038
22 Biliran H Jr, Sheng S. Pleiotrophic inhibition of pericellular urokinase-type plasminogen activator system by endogenous tumor suppressive Maspin. *Cancer Res* 2001; 61: 8676-8682
23 Zhang W, Zhang M. Tissue microarray analysis of Maspin expression and its reverse correlation with mutant p53 in various tumors. *Int J Oncol* 2002; 20: 1145-1150
24 Cher ML, Biliran HR Jr, Bhagat S, Meng Y, Che M, Lockett J, Abrams J, Fridman R, Zachareas M, Sheng S. Maspin expression inhibits osteolysis, tumor growth, and angiogenesis in a model of prostate cancer bone metastasis. *Proc Natl Acad Sci USA* 2003; 100: 7847-7852
25 Kitoh T, Yanai H, Saitoh Y, Nakamura Y, Matsubara Y, Kitoh H, Yoshida T, Okita K. Increased expression of matrix metalloproteinase-7 in invasive early gastric cancer. *J Gastroenterol* 2004; 39: 434-440
26 Ajisaka H, Yonemura Y, Miwa K. Correlation of lymph node metastases and expression of matrix metalloproteinase-7 in patients with gastric cancer. *Hepatogastroenterology* 2004; 51: 900-905
27 Chen JQ, Zhan WH, He YL, Peng JS, Wang JP, Cai SR, Ma JP. Expression of heparanase gene, CD44v6, MMP-7 and nm23 protein and their relationship with the invasion and metastasis of gastric carcinomas. *World J Gastroenterol* 2004; 10: 776-782
28 Aihara R, Mochiki E, Nakabayashi T, Akazawa K, Asao T, Kuwano H. Clinical significance of mucin phenotype, beta-catenin and matrix metalloproteinase 7 in early undifferentiated gastric carcinoma. *Br J Surg* 2005; 92: 454-462
29 Festuccia C, Angelucci A, Gravina G, Eleuterio E, Vicentini C, Bologna M. Bombesin-dependent pro-MMP-9 activation in prostatic cancer cells requires beta1 integrin engagement. *Exp Cell Res* 2002; 280: 1-11
30 Salgado S, Garcia J, Vera J, Siller F, Bueno M, Miranda A, Segura A, Grijalva G, Segura J, Orozco H, Hernandez-Pando R, Fafutis M, Aguilar LK, Aguilar-Cordova E, Armendariz-Borunda J. Liver cirrhosis is reverted by urokinase-type plasminogen activator gene therapy. *Mol Ther* 2000; 2: 545-551

电编 张敏 编辑 潘伯荣