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临床经验 CLINICAL PRACTICE

食管癌MMP基因高表达与临床病理特征的关系

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■背景资料
肿瘤侵袭和转移必须获得降解细胞外基质突破组织屏障的能力, 基质金属蛋白酶系列是降解细胞外基质蛋白的最重要的一组蛋白水解酶, 可能在肿瘤的侵袭转移过程中起重要作用. 本文结合近年来国内外一些最新的实验报道对MMP与肿瘤侵袭和转移的关系进行观察, 为其进一步的研究和应用提供基本资料.

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Relationship between expression of matrix metalloproteinase and clinicopathological characteristics in esophageal carcinoma

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Abstract

AIM: To study the expression of matrix metalloproteinases (MMP-2, MMP-7, and MMP-9) and their correlations with clinicopathological characteristics in esophageal carcinoma.

METHODS: The expression of MMP-2, MMP-7, and MMP-9 mRNA were detected in 48 cases of esophageal carcinoma and cancer-adjacent tissues by the reverse transcriptase polymerase chain reaction (RT-PCR).

RESULTS: The expression of MMP-2, MMP-7, and MMP-9 were significantly higher in esophageal carcinoma tissues than those in cancer-adjacent ones, respectively (χ^2 = 5.978, 19.045, 5.440; P < 0.05-0.001). The expression of MMP was markedly correlated with the tumor size (r = 0.84, 0.70, 0.48; P < 0.05-0.001), degree of differentiation (r = 0.89, 0.57, 0.91; P < 0.05), and clinical staging (r = 0.81, 0.73, 0.61; P < 0.05). MMP-2 expression was also notably correlated with lymph node metastasis (r = 0.048, P < 0.05).

CONCLUSION: The over-expression of MMP is correlated with the carcinogenesis, development and metastasis of esophageal carcinoma, which can be used as important indexes to judge the invasion and metastasis of esophageal carcinoma.

Key Words: Esophageal carcinoma; Matrix metalloproteinase; Pathology

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摘要

目的: 探讨MMP-2, MMP-7, MMP-9基因在食管癌和癌旁组织中的表达以及与食管癌各临床病理指标之间的关系.

方法: 采用RT-PCR方法分别检测48例食管癌及癌旁组织MMP-2、MMP-7、MMP-9 mRNA的阳性表达率及含量.

结果: 在食管癌组织中MMP-2, MMP-7, MMP-9的阳性表达率分别为81.3%, 62.5%和75.0%, 明显高于癌旁组织的58.3%, 18.8%和52.1%, 两两比较差异均有显著性(χ^2 = 5.978, 19.045, 5.440; P<0.05-0.001). MMP-2, MMP-7, MMP-9表达与肿瘤的大小(r = 0.84, 0.70, 0.48; P<0.05-0.001)、分化高低(r = 0.89, 0.57, 0.91; P<0.05)及临床分期(r = 0.81, 0.73, 0.61; P<0.05)有关, MMP-2 mRNA表达量的高低与淋巴结是否转移有关(r = 0.048, P<0.05).

结论: 食管癌组织MMP-2, MMP-7, MMP-9高表达与食管癌的发生、发展及淋巴结转移有关, 可作为预测肿瘤转移潜能的指标.

关键词: 食管癌; 基质金属蛋白酶; 病理

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■研发前沿
肿瘤的发生发展、侵袭和转移涉及许多因素, 而MMP是此过程中的限速酶, 在中性PH环境下, 能降解结缔组织分解细胞外基质(细胞间基质和基底膜)所有的大分子蛋白, 所以他们的活性与肿瘤的侵袭和转移有密切关系, 因此,进一步研究MMP与肿瘤侵袭和转移的关系, 可能成为其下一步研究的前沿和热点.

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0 引言

食管癌是我国常见消化道恶性肿瘤之一[1], 其侵袭转移是一个复杂的过程, 与多个基因和多个分子水平变化密切相关[2-9], 肿瘤侵袭和转移必须获得降解细胞外基质突破组织屏障的能力, 已证明基质金属蛋白酶(matrix metalloproteinase, MMP)系列是降解细胞外基质蛋白的最重要的一组蛋白水解酶[7], Ⅳ型胶原酶(包括MMP-2和MMP-9)和基质溶解素(MMP-7)是MMP家族的重要成员, 可能在肿瘤的侵袭转移过程中起重要作用. 我们采用RT-PCR方法观察MMP-2、MMP-9和MMP-7在食管癌组织和癌旁组织中的表达以及与各临床病理指标之间的关系, 以探讨其表达量的变化与食管癌侵袭转移及预后的关系. 旨为预测食管癌转移潜能和评估预后寻求一个新的生物学指标.

1 材料和方法

1.1 *材料* 2001-06/2002-06因食管癌行根治切除并经病理证实的食管癌组织48例. 男36例, 女12例, 年龄36-84(平均59.7±11.4)岁. 病理确诊均为鳞癌. 早期12例, 中晚期36例; 淋巴结转移31例, 无转移17例. 术中取无菌标本, 放入经消毒处理的小瓶内, -80℃储存备用.

1.2 *方法* 用D-Hanks液清洗组织标本, 然后用无菌眼科剪剪碎至直经约1 mm组织小块. 加胰蛋白酶和胶原酶消化. 将肿瘤组织和癌旁组织制成单细胞悬液, 用Trizol试剂进一步提取细胞总RNA. 紫外分光光度计定量. MMP-2, MMP-7和MMP-9 mRNA的检测采用RT-PCR方法. 取1 μg细胞总RNA, 采用逆转录试剂盒要求的标准条件进行RNA逆转录反应, 所获cDNA用作PCR反应的模板. MMP-2, MMP-7, MMP-9和内参照β2-actin基因引物分别参照文献[10-11]设计, 引物序列如下: MMP-2引物上游为: 5'-ACA AAG AGT GGC AGT GCA A-3', 下游为: 5'-CAC GAG CAA AGG CAT CC-3'; MMP-7引物上游为: 5'-AGA TGT GGA GTG CCA GAT GT-3', 下游为: 5'-TAG ACT GCT ACC ATC CGT CC-3'; MMP-9引物上游为: 5'-GCC TGC CAC TTC CCC TTC ATC-3', 下游为: 5'-CCC CAC TTC TTG TCG CTG TCA-3'; β2-actin引物上游为: 5'-CTG TCT GGC GGC ACC ACC AT-3', 下游为: 5'-GCA ACT AAG TCA TAG CCG C-3'. 上述引物扩增片段长度分别为302 bp, 365 bp, 476 bp和254 bp, 由上海生工技术服务有限公司合成. 对PCR反应条件进行优化确定最适浓度和其他各反应成分浓度, 全部实验按最佳优化条件进行, 在同一反应体系对MMP-2和β2-actin, MMP-7和β2-actin, MMP-9和β2-actin 3对基因分别同时扩增, 扩增条件为95℃变性30 s, 57℃复性30 s, 72℃延伸1 min, 共33个循环, 最后72℃延伸2 min. 取10 μL扩增产物于含EB(0.5 mg/L)的20 g/L的琼脂糖凝胶中电泳, 80 V, 1 h, 紫外透射仪下观察结果并照相. 在激光密度扫描仪上扫描底片, 若观察到特异性扩增条带者, 表明MMP基因阳性表达, 若无特异性扩增条带则视为无MMP基因表达. 用MMP峰面积与β2-actin峰面积的比值表示MMP基因的表达水平.

统计学处理 采用 SPSS 11.0统计软件.

表 1 MMP-2, MMP-7和MMP-9与临床病理的关系 (mean ± SD)

临床病理	*n*	MMP-2	MMP-7	MMP-9
食管癌组织	48	0.99 ± 0.48	0.87 ± 0.23	1.20 ± 0.37
癌旁组织	48	0.51 ± 0.41[b]	0.23 ± 0.08[b]	0.53 ± 0.42[b]
肿瘤大小				
<5 cm	16	0.43 ± 0.33	0.31 ± 0.44	0.50 ± 0.34
≥5 cm[a]	32	0.99 ± 0.36	0.75 ± 0.32	0.82 ± 0.67
分化程度				
高分化	14	0.30 ± 0.32	0.18 ± 0.30	0.34 ± 0.45
低分化[a]	34	0.84 ± 0.44	0.75 ± 0.41	0.93 ± 0.54
临床分期				
早期	12	0.39 ± 0.29	0.32 ± 0.34	0.30 ± 0.32
中晚期[a]	36	1.15 ± 0.43	0.95 ± 0.42	0.92 ± 0.38
淋巴结转移				
有	17	1.19 ± 0.383	0.91 ± 0.40	1.16 ± 0.42
无	31	0.44 ± 0.38[a]	0.35 ± 0.37	0.40 ± 0.41

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

2 结果

2.1 MMP-2, MMP-7和MMP-9的表达 MMP-2在48例食管癌组织中的阳性例数为39例, 阳性率81.3%, 在癌旁组织中的阳性例数28例, 阳性率为58.3%, 两者之间有显著性差异(χ^2 = 5.978, P = 0.014); MMP-7在癌组织中的阳性例数为30例, 阳性率为62.5%, 在癌旁组织中的阳性例数为9例, 阳性率为18.8%, 两者之间有显著性差异(χ^2 = 19.045, P = 0.000); MMP-9在40例食管组织中的阳性例数为36例, 阳性率75.0%, 在癌旁组织中的阳性例数25例, 阳性率为52.1%, 两者之间有显著性差异(χ^2 = 5.440, P = 0.020). MMP-2, MMP-9和MMP-7 mRNA表达量显著高于其癌旁

■应用要点
本文观察食管癌组织和癌旁组织中的表达以及与各临床病理指标之间的相关性, 以探讨其表达量的变化与食管癌侵袭转移及预后的关系, 为食管癌的治疗提供依据.

■同行评价
作者在文中将MMP与肿瘤侵袭和转移的关系做进一步研究, 选题意义热门, 学术价值较高, 文字质量良, 文献引用可, 有一定的学术价值和新颖性, 综合水平良好.

组织(P<0.01, 表1).

2.2 MMP-2, MMP-7和MMP-9与临床病理指标的关系 MMP-2, MMP-7和MMP-9 mRNA表达量与肿瘤的大小(r = 0.84; r = 0.70; r = 0.48; P<0.05-0.001)、分化高低(r = 0.89; r = 0.57; r = 0.91; P<0.05)及临床分期(r = 0.81; r = 0.73; r = 0.61; P<0.05)有关, MMP-2 mRNA表达量的高低与淋巴结是否转移有关(r = 0.048, P＜0.05), 合并有淋巴结转移的17例胃癌患者MMP-2 mRNA表达量明显高于不伴有淋巴结转移的胃癌患者(表1).

3 讨论

肿瘤侵袭和转移必须获得降解细胞外基质(extracellular matrix, ECM)突破组织屏障的能力, 细胞外基质主要由胶原、糖蛋白、蛋白多糖和氨基葡萄糖组成, 以基底膜和间质结缔组织形式存在. 胶原是细胞外基质的主要成分, Ⅰ, Ⅱ, Ⅲ型胶原主要存在于间质结缔组织, Ⅳ型胶原主要存在于基底膜. 肿瘤细胞通过已存在的或新形成的结合位点与细胞外基质结合, 进而溶解细胞外基质, 最后经细胞外基质的缺损处向外转移. 肿瘤的发生、发展、侵袭和转移涉及许多因素, 而MMP是此过程中的限速酶, 在中性pH环境下, 能降解结缔组织分解细胞外基质(细胞间基质和基底膜)所有的大分子蛋白, 所以他们的活性与肿瘤的侵袭和转移有密切关系[12-21]. 有研究发现, 单一MMP-2或/和MMP-9或MMP-7可能与原发性肝癌、膀胱癌、结肠癌、胃癌等[22-28]的侵袭和转移性有关, 但多种MMP与食管癌侵袭转移性的关系未见报道. 本研究采用先进的RT-PCR方法除对食管癌及癌旁组织中MMP-2、MMP-7和MMP-9进行定性表达外, 还对MMP-2、MMP-7和MMP-9 mRNA进行定量测定. 结果显示, 在食管癌组织中MMP-2、MMP-9和 MMP-7的阳性表达率均较癌旁组织为高, 有癌旁组织表达的基本见于分化差且临床分期较高的食管癌病例. 分化好或早期食管癌, 癌组织及癌旁组织阳性表达者较少. 从而提示基质金属蛋白酶在食管癌的发生、发展中可能起到某些重要的作用, 其活性的阳性检出率可作为食管癌的诊断指标之一. 食管癌组织MMP-2、MMP-7和MMP-9吸光度值较癌旁组织明显增高, 说明癌组织通过表达量的变化来增加其侵袭性. 癌旁组织虽较癌组织中表达量低, 但仍有一定的表达能力, 提示肿瘤细胞可以通过可溶介质或膜黏合分子与间质细胞进行信息交换, 协同产生和调节MMP, 这在肿瘤细胞侵袭和转移机制中可能具有重大意义.

肿瘤组织中MMP-2、MMP-9和 MMP-7与临床病理因素和预后的关系, 本研究发现食管癌组织中MMP-2、MMP-9和MMP-7的含量与肿瘤的大小有关, 这可能是由于瘤体增大时, 瘤体的血供相对不足, 从而使与癌细胞侵袭相关的功能基因表达增加, 以便逃离血供不足的环境而向远处血供丰富的地方侵犯, 而MMP-2、MMP-9和 MMP-7是重要的与侵袭相关的功能基因, 因此其表达随着胃癌瘤体的增大而增加[29]. 这点有助于食管癌的早期诊断及早期治疗. MMP-2、MMP-7和MMP-9的过度表达与转移性肿瘤细胞的局部浸润和扩散之间具有很密切的关系[30-38], 我们发现中晚期食管癌MMP-2、MMP-7和MMP-9的表达量明显高于早期食管癌, 有淋巴结转移和远处转移者明显高于非转移的食管癌患者, 提示MMP系列不仅在食管癌侵袭及转移过程中发挥重要的作用, 且与食管癌的预后密切有关, 可作为临床预测肿瘤侵袭转移潜能的指标之一.

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·消息·

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·消息·

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