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MMP-2、MMP-7、MMP-9、TIMP-1 及 TIMP-2 在乳腺癌组织中的表达及意义

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摘要 目的:探讨基质金属蛋白酶及其抑制剂在乳腺癌组织中的表达及其与肿瘤浸润转移的关系,为乳腺癌的临床治疗及预后预测提供基础。**方法:**选择我院 2012 年 5 月至 2014 年 5 月收治的乳腺癌患者 80 例,对所选病例的乳腺癌组织、癌旁组织及正常乳腺组织样本进行检测。观察并比较不同乳腺组织中 MMP-2、MMP-7、MMP-9、TIMP-1 及 TIMP-2 mRNA 的表达水平。**结果:**与正常乳腺组织相比较,乳腺癌组织和癌旁组织中 MMP-2、MMP-7、MMP-9、TIMP-1 及 TIMP-2 mRNA 的表达显著增加,差异具有统计学意义($P<0.05$)。乳腺癌组织中 MMP-2、MMP-7、MMP-9、TIMP-1 及 TIMP-2 mRNA 的表达显著高于癌旁组织和正常组织,差异具有统计学意义 ($P<0.05$)。随着肿瘤范围扩大,MMP-2、MMP-7 和 MMP-9 mRNA 的表达水平显著增加 ($P<0.05$),而 TIMP-1 和 TIMP-2 mRNA 表达无显著变化($P>0.05$)。随着淋巴结转移进展,MMP-2、MMP-7 和 MMP-9 mRNA 的表达显著增加($P<0.05$),而 TIMP-1 和 TIMP-2 mRNA 无显著变化($P>0.05$)。**结论:**MMP-2、MMP-7、MMP-9、TIMP-1 和 TIMP-2 的 mRNA 在乳腺癌组织中呈高表达,这可能与乳腺癌的发生和发展有关,而 MMP-2、MMP-7 和 MMP-9 可能有助于预测乳腺癌的侵袭行为。

关键词:基质金属蛋白酶;基质金属蛋白酶抑制剂;乳腺癌;浸润转移

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Expressions and Significances of MMP-2, MMP-7, MMP-9, TIMP-1 and TIMP-2 mRNAs in the Breast Cancer

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ABSTRACT Objective: To explore the expressions of MMPs and TIMPs in the tissues of breast cancer and their relationships with tumor metastasis in order to provide references for the treatment and prognostic prediction of breast cancer. **Methods:** 80 patients with breast cancer who were treated in our hospital from May 2012 to May 2014 were selected. Then the mRNA expressions of MMP 2, MMP-7, MMP-9, TIMP 1 and TIMP-2 in breast cancer, para-carcinoma tissue and normal breast tissues were detected and compared. **Results:** Compared with that in the normal breast tissues, the mRNA expressions of MMP 2, MMP-7, MMP-9, TIMP 1 and TIMP-2 in the breast cancer and para-carcinoma tissue were all significantly increased ($P<0.05$). The mRNA expressions of MMP 2, MMP-7, MMP-9, TIMP-1 and TIMP-2 in the breast cancer tissues and the para-carcinoma tissue were significantly higher than those of the control group($P<0.05$). With the increase of tumor range, the mRNA expression of MMP-2, MMP-7 and MMP-9 were all significantly increased ($P<0.05$), and no significant difference was found in the mRNA expression of TIMP-1 and TIMP-2 ($P>0.05$). With the progression of lymph node metastasis, the mRNA expressions of MMP-2, MMP-7 and MMP-9 were all significantly increased ($P<0.05$), and no significant difference was found in the mRNA expression of TIMP-1 and TIMP-2 ($P>0.05$). **Conclusions:** MMP 2, MMP-7, MMP-9 and TIMP 1 and TIMP-2 mRNA were highly expressed in breast cancer tissue, which could be closely related to the occurrence and development of breast cancer. MMP 2, MMP-7 and MMP-9 may be useful for the prediction of infiltration and metastasis of breast cancer.

Key words: MMPs; TIMPs; Breast cancer; Infiltration and metastasis

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前言

乳腺癌(breast cancer)是发生在乳腺腺上皮组织的恶性肿瘤,其临床表现与肿瘤分期有关。近年来,乳腺癌的发病率逐年升高,且倾向于年轻女性,严重威胁着女性的身心健康^[1-3]。随着

分子生物学技术和循证医学的进步,乳腺癌的治疗已从单纯手术切除发展成放疗、化疗、内分泌治疗和靶向治疗相结合的综合治疗模式。虽然这些治疗方法对早期乳腺癌具有一定的疗效,但乳腺肿瘤的复发转移率依然很高,且预后较差^[4-6]。因此,开发一种特异性强的新型分子靶点对乳腺癌的早期诊断及预后至关重要。

基质金属蛋白酶(matrix metalloproteinases, MMPs)是一组依赖二价金属阳离子的内肽酶。基质金属蛋白酶抑制剂(tissue

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inhibitor of metalloproteinases, TIMPs) 是重要的内源性调节因子,能够抑制 MMPs 的活性^[7,8]。大量研究证明,基质金属蛋白酶及其抑制剂在肿瘤的发生及发展过程中发挥重要作用^[9,10]。本研究主要探讨了 MMPs 和 TIMPs 与乳腺癌发生及发展的关系,结果如下。

1 资料与方法

1.1 一般资料

选择我院 2012 年 5 月至 2014 年 5 月收治的乳腺癌患者 80 例,年龄 33-62 岁,平均 (45.18 ± 2.55) 岁。肿瘤大小:T1 期 32 例(肿瘤直径 ≤ 2 cm),T2 期 29 例(肿瘤直径 >2 cm 且 ≤ 5 cm),T3 期 16 例(肿瘤直径 >5 cm),T4 期 3 例(肿瘤浸润或转

移)。淋巴结转移:N0 期 37 例,N2 期 28 例,N3 期 11 例,N4 期 4 例。病理类型:浸润性导管癌 25 例,浸润性小叶癌 28 例,乳头状癌 17 例,髓样癌 10 例。本研究均取得患者知情同意,且经过伦理委员会批准。

1.2 Real-time PCR

严格按照 PCR 试剂盒(日本 TaKaRa 公司)说明书提取 RNA,逆转录获得 cDNA,将 cDNA 扩增为 MMP-2、MMP-7、MMP-9、TIMP-1 和 TIMP-2,内参用 β -actin。PCR 反应条件:95 $^{\circ}\text{C}$ 30 s,95 $^{\circ}\text{C}$ 5 s,60 $^{\circ}\text{C}$ 45 s,共 42 个循环。采用 $2^{-\Delta\Delta\text{CT}}$ 法对 mRNA 表达相对强度进行分析。实验重复 3 次,取平均值。引物序列见表 1。

表 1 PCR 的引物序列
Table 1 Primer sequences of PCR

	Forward primer	Reverse primer
MMP-2	ATTTCCCCTCGACAGCCTC	GTCCCAGGCGTAGACCAATA
MMP-7	AGTCCACTGAGTAGCGCAGC	CATATCACGCATCTGGGGTC
MMP-9	AATATCAGACATTCGGGAGG	GTCAATGTACAGCTGCCCA
TIMP-1	AAATGTACAGCTGCCGTACC	CAATGTACAGCTGCCGTACG
TIMP-2	ATCAATGTACAGCTGCGTAG	CTAGGTAAAGGCTGTAGTAC
β -actin	GTCGGTGAATGAAGTGCTTA	GCTTCGGGTAAAGTTTGCCGG

1.3 统计学分析

所有数据均使用 SPSS13.0 软件进行统计处理,计数资料用均值 $\pm$ 标准差表示,两组正态分布的资料采用配对 T 检验,以 $P<0.05$ 为差异有统计学意义。

2 结果

2.1 乳腺癌组织、癌旁组织及正常乳腺组织中 MMPs 和 TIMPs mRNA 的表达

如表 2 所示,MMP-2、MMP-7、MMP-9、TIMP-1 和 TIMP-2 mRNA 在乳腺癌组织中的表达水平分别为 (0.42 ± 0.04) 、 (0.47 ± 0.07) 、 (0.58 ± 0.02) 、 (0.29 ± 0.05) 和 (0.16 ± 0.06) ;在乳腺癌癌旁组织中的表达水平分别为 (0.29 ± 0.02) 、 (0.28 ± 0.04) 、

(0.36 ± 0.06) 、 (0.17 ± 0.05) 和 (0.15 ± 0.03) ;在乳腺正常组织中的表达水平分别为 (0.14 ± 0.03) 、 (0.18 ± 0.09) 、 (0.26 ± 0.06) 、 (0.08 ± 0.03) 和 (0.06 ± 0.02) 。

与正常乳腺组织相比较,乳腺癌组织和癌旁组织中 MMP-2、MMP-7、MMP-9、TIMP-1 及 TIMP-2 mRNA 的表达水平均显著增加,差异具有统计学意义($P<0.05$)。乳腺癌组织中 MMP-2、MMP-7、MMP-9、TIMP-1 及 TIMP-2 mRNA 的表达显著高于癌旁组织和正常乳腺组织,差异具有统计学意义($P<0.05$)。

2.2 不同分期乳腺癌组织中 MMPs 与 TIMPs mRNA 的表达

随着肿瘤范围逐渐扩大,MMP-2、MMP-7 和 MMP-9 mRNA 的表达水平显著增加,差异具有统计学意义($P<0.05$);而

表 2 乳腺癌组织、癌旁组织及正常乳腺组织中 MMPs 和 TIMPs mRNA 的表达比较

Table 2 Comparison of the Mrna Expressions of MMPs and TIMPs in breast cancer, para-carcinoma tissue and normal breast tissues

Indicators	Tumor tissues	Adjacent tissues	Normal tissues
MMP-2	$0.42 \pm 0.04^{**}$	$0.29 \pm 0.02^{*}$	0.14 ± 0.08
MMP-7	$0.47 \pm 0.07^{**}$	$0.28 \pm 0.04^{*}$	0.18 ± 0.05
MMP-9	$0.58 \pm 0.02^{**}$	$0.36 \pm 0.06^{*}$	0.16 ± 0.06
TIMP-1	$0.29 \pm 0.05^{**}$	$0.17 \pm 0.05^{*}$	0.08 ± 0.03
TIMP-2	$0.26 \pm 0.06^{**}$	$0.15 \pm 0.03^{*}$	0.06 ± 0.02
β -actin	$0.16 \pm 0.08^{**}$	$0.13 \pm 0.07^{*}$	0.07 ± 0.04

注:与正常乳腺组织比较,* $P<0.05$;与癌旁组织和正常乳腺组织比较, $^{*}P<0.05$ 。

Note: compared with normal tissues, * $P<0.05$; compared with the para-carcinoma tissue and normal breast tissues, $^{*}P<0.05$.

TIMP-1 和 TIMP-2 mRNA 的表达无显著性差异($P>0.05$)。随着淋巴结转移的进展, MMP-2、MMP-7 和 MMP-9mRNA 的表达水平显著增加, 差异具有统计学意义 ($P<0.05$); 而 TIMP-1 和 TIMP-2 mRNA 的表达无显著性差异($P>0.05$)。见表 3。

表 3 不同分期乳腺癌组织中 MMPs 和 TIMPs mRNA 的表达比较

Table 3 Comparison of the expressions of MMPs and TIMPs mRNA between different clinical stages of breast cancer

Indicators	Tumor size				Lymph node metastasis			
	T1(n=32)	T2(n=29)	T3(n=16)	T4(n=3)	N0 (n=37)	N1(n=28)	N2(n=11)	N3(n=4)
MMP-2	0.23± 0.06	0.49± 0.03	0.61± 0.06	0.65± 0.09*	0.24± 0.05	0.50± 0.02	0.58± 0.06	0.65± 0.07*
MMP-7	0.38± 0.03	0.56± 0.02	0.62± 0.05	0.71± 0.06*	0.23± 0.03	0.54± 0.05	0.63± 0.05	0.72± 0.06*
MMP-9	0.38± 0.07	0.66± 0.04	0.75± 0.07	0.90± 0.07*	0.31± 0.02	0.69± 0.03	0.80± 0.08	0.87± 0.02*
TIMP-1	0.16± 0.09	0.16± 0.06	0.16± 0.07	0.15± 0.08 [#]	0.15± 0.08	0.16± 0.01	0.16± 0.05	0.16± 0.06 [#]
TIMP-2	0.17± 0.07	0.16± 0.08	0.17± 0.06	0.18± 0.09 [#]	0.16± 0.03	0.16± 0.07	0.16± 0.06	0.16± 0.07 [#]

注:差异显著, * $P<0.05$;无显著差异, [#] $P>0.05$ 。

Note: significant differences, * $P<0.05$; no significant difference, [#] $P<0.05$.

3 讨论

恶性肿瘤的侵袭和转移过程非常复杂,其中至关重要是肿瘤组织中具有调节细胞增殖与凋亡功能的相关因子呈异常表达而导致了凋亡过程的失控^[11]。因此,针对增殖凋亡相关基因及其表达产物与肿瘤关系的深入研究有助于揭示肿瘤的发病机制,对早期诊断、预防以及治疗肿瘤均具有重要的临床意义。

MMP-2 基因位于人类染色体 16q21,由 13 个外显子和 12 个内含子所组成,结构基因总长度为 27kb,与其他金属蛋白酶不同,MMP-2 基因 5' 旁侧序列促进子区域含有 2 个 GC 盒而不是 TATA 盒^[12]。MMP-9 是以酶原的形式从胞内分泌到胞外,不仅能降解 IV 型胶原及纤维粘连蛋白等基底膜和细胞外基质成分,对肿瘤细胞的黏附能力也具有一定影响,在肿瘤的生长、浸润、转移过程中发挥重要作用^[13]。相关研究显示乳腺癌组织中 MMP-2、MMP-9 的活性显著高于纤维腺瘤;乳腺癌患者中,浸润性癌及淋巴结转移组的 MMP-2、MMP-9 的活性显著高于非浸润性癌及无淋巴结转移组^[14,15]。有研究发现,MMP-7 在人类乳腺癌中的表达异常并且 MMP-7 的消除与肿瘤生长缓慢和低侵袭性相关^[16]。还有研究表明 MCF-7 在乳腺癌细胞的过度表达可增强细胞的浸润和前 MMP-2 和 MMP-9 的活化^[17]。本研究表明,乳腺癌组织中 MMP-2、MMP-7 和 MMP-9 的 mRNA 表达明显高于在正常乳腺组织,且伴随肿瘤的扩大和淋巴结转移,MMP-2、MMP-7 和 MMP-9 的 mRNA 表达显著增加,提示 MMP-2、MMP-7 和 MMP-9 异常表达与乳腺癌的浸润转移有关。

金属蛋白酶组织抑制因子(TIMPs)是 MMPs 家族的组织抑制剂,广泛分布于组织和体液中,共价结合 MMPs 而抑制其活性。TIMP-1 作为 MMP-9 的抑制剂,与 MMP-9 的酶原或活化后酶的催化区的羧基末端特异性结合,形成复合物,从而特异性抑制 MMP-9 的活性^[20]。乳腺癌属于上皮性肿瘤,具有很强的侵袭转移潜能。既往研究证实,MMPs 和 TIMPs 在大肠癌、胃癌及胰腺癌等多种肿瘤组织中呈异常表达,对肿瘤的转移和侵袭具体推动作用^[18]。基底膜基质降解与各种亚型 MMPs 的活动以

及相应的基质金属蛋白酶抑制剂 (TIMPs) 组织有着紧密联系^[19]。本研究结果显示乳腺癌中的 TIMP-1 和 TIMP-2 的 mRNA 表达明显高于正常乳腺组织,表明 TIMP-1 和 TIMP-2 的高表达与乳腺癌的发生密切相关。

综上所述,MMP-2、MMP-7、MMP-9、TIMP-1 和 TIMP-2 的 mRNA 表达在乳腺癌中明显呈高表达,可能与乳腺癌的发生和发展有关,而 MMP-2、MMP-7 和 MMP-9 可能有助于预测乳腺癌的侵袭行为。

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