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乳腺导管原位癌和浸润性导管癌中 MMP-7、VEGF 及 E-cad 的表达及临床意义 *

刘国军[1] 吴小蔚[1△] 孙圣荣[1] 毛哲玉[2] 张书卿[2]

（1 武汉大学人民医院整形外科 湖北 武汉 430060；2 鄂东医疗集团黄石市中心医院乳甲肿瘤外科 湖北 武汉 435000）

摘要 目的：探讨乳腺导管原位癌（DCIS）和浸润性导管癌（IDC）中基质金属蛋白酶 -7（MMP-7）、血管内皮生长因子（VEGF）及钙黏附素 E（E-cad）的表达及临床意义。**方法：**选取 2012 年 1 月 -2017 年 8 月期间鄂东医疗集团黄石市中心医院乳甲外科的 DCIS 石蜡包埋标本（DCIS 组）59 例，IDC 石蜡包埋标本（IDC 组）32 例，另选取同时期正常乳腺组织标本 20 例为对照组，检测各组 MMP-7、VEGF 及 E-cad 的表达情况，并分析 MMP-7、VEGF 及 E-cad 的阳性表达率与 DCIS、IDC 患者临床病理特征的关系，采用 Pearson 相关性分析 MMP-7、VEGF 与 E-cad 之间的相关性。**结果：**DCIS 组、IDC 组的 MMP-7、VEGF 阳性表达率高于对照组，E-cad 的强阳性表达率低于对照组（P<0.05），DCIS 组与 IDC 组之间的 MMP-7、VEGF、E-cad 阳性表达率比较差异无统计学意义（P>0.05）。MMP-7、VEGF 及 E-cad 的阳性表达率均与患者的年龄、肿瘤大小无关（P>0.05），临床分期为 II-III 期、中 / 低分化程度、有淋巴结转移患者的 MMP-7、VEGF 的阳性表达率高于临床分期为 I 期、高分化程度、无淋巴结转移患者（P<0.05），中 / 低分化程度、有淋巴结转移患者的 E-cad 的阳性表达率低于高分化程度、无淋巴结转移患者（P<0.05）。经 Pearson 相关性分析显示，MMP-7 与 VEGF 存在正相关关系（r=0.362，P=0.038），MMP-7、VEGF 均与 E-cad 无显著相关性（r=0.071、0.024，P=0.057、0.089）。**结论：**DCIS 和 IDC 中 MMP-7、VEGF 表达较高，E-cad 表达较低，且与患者临床分期、分化程度、淋巴结转移有关，临床上可以通过检查 MMP-7、VEGF、E-cad 的表达来评估乳腺癌的发生及发展。

关键词：乳腺导管原位癌；浸润性导管癌；基质金属蛋白酶 -7；血管内皮生长因子；钙黏附素 E

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Expressions and Clinical Significance of MMP-7, VEGF and E-cad in Breast Ductal Carcinoma in Situ and Invasive Ductal Carcinoma*

LIU Guo-jun[1], WU Xiao-wei[1△], SUN Sheng-rong[1], MAO Zhe-yu[2], ZHANG Shu-qing[2]

(1 Department of Plastic Surgery, Renmin Hospital of Wuhan University, Wuhan, Hubei, 430060, China;

2 Surgical Oncology Department of Thyroid and Breast, Huangshi Central Hospital, Edong Healthcare, Wuhan, Hubei, 435000, China)

ABSTRACT Objective: To investigate the expressions and clinical significance of Matrix metalloproteinase -7 (MMP-7), vascular endothelial growth factor (VEGF) and Calcium adherent E (E-cad) in breast ductal carcinoma in situ (DCIS) and invasive ductal carcinoma(IDC). **Methods:** 59 cases of DCIS paraffin embedded specimens (DCIS group), 32 cases of IDC paraffin embedded specimens (IDC group) in Hubei Medical Group of breast and thyroid surgery of Huangshi Central Hospital from January 2012 to August 2017 were selected, 20 cases of normal breast tissue samples during the same period were selected as control group. The expressions of MMP-7, VEGF and E-cad in each group were detected. The relationship between the positive expression rates of MMP-7, VEGF and E-cad and the clinicopathological features of patients with DCIS and IDC were analyzed. The correlation between MMP-7, VEGF and E-cad were analyzed by Pearson correlation. **Results:** The positive expression rates of MMP-7 and VEGF in DCIS group and IDC group were higher than those in the control group, the strong positive expression rate of E-cad was lower than that in the control group (P<0.05); there was no significant difference in the positive expression rate of MMP-7, VEGF and E-cad between DCIS group and IDC group (P>0.05). The positive rates of MMP-7, VEGF and E-cad were not related to the age of the patients and the size of the tumor (P>0.05). The positive expression rates of MMP-7 and VEGF in the patients with II-III stage, intermediate / low degree of differentiation and lymph node metastasis were higher than those of the patients with I stage, high differentiation degree and no lymph node metastasis (P<0.05). The positive rate of E-cad in patients with moderate / low differentiation and lymph node metastasis was lower than those of patients with high differentiation and no lymph node metastasis (P<0.05). Pearson correlation analysis showed that there was a positive correlation between MMP-7 and VEGF(r=0.362, P=0.038), MMP-7 and VEGF were not significantly correlated with E-cad (r=0.071,0.024,P=0.057, 0.089). **Conclusion:** The expressions of MMP-7 and VEGF in DCIS group and IDC group are higher, but the expression of E-cad is

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作者简介：刘国军（1975-），男，本科，副主任医师，从事肿瘤外科方面的研究，E-mail：qeigne@163.com

△ 通讯作者：吴小蔚（1969-），男，博士，主任医师，从事整形外科方面的研究，E-mail：yweogh@163.com

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lower, which is related to the clinical stage, degree of differentiation and lymph node metastasis of the patients. The development of breast cancer can be evaluated by examining the expressions of MMP-7, VEGF and E-cad.

Key words: Ductal carcinoma in situ; Invasive ductal carcinoma; Matrix metalloproteinase; Vascular endothelial growth factor; Calcium adherent E

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前言

乳腺癌是临床常见的女性恶性肿瘤，其发病率在全球女性恶性肿瘤中占据首位，近年来，随着人们生活方式的改变及社会压力的增加，乳腺癌的发病率呈逐年上升的趋势，且发病人群趋于年轻化，对女性的生命健康造成了严重威胁[1-3]。有研究报道，乳腺癌的发生及发展与肿瘤细胞间粘附能力降低、胞外基质的降解及肿瘤新血管形成等关系密切[4-6]。血管内皮生长因子（vascular endothelial growth factor, VEGF）可通过增加血管通透性、促进血管内皮增殖及抑制肿瘤细胞凋亡等促进肿瘤的浸润、生长及转移，是目前临床上作用最强的促血管生长因子[7,8]。基质金属蛋白酶 7（matrix metalloproteinase, MMP-7）在各种肿瘤细胞中均有表达，是基质金属蛋白酶中分子质量最小的一种，可以降解酪蛋白、蛋白聚糖及层黏连蛋白等，促进肿瘤细胞穿透基底膜，使其能向肿瘤周围组织转移和浸润[9,10]。钙黏附素 E（E-cadherin，E-cad）是一种细胞间黏附分子，近年来，随着对肿瘤细胞黏附功能的研究显示 [11]，E-cad 在多种癌细胞系或癌组织中的表达水平下降，细胞黏附功能发生障碍。本研究主要对乳腺导管原位癌（ductal carcinoma in situ，DCIS）和浸润性导管癌（infitrating ductal carcinoma，IDC）中 MMP-7、VEGF、E-cad 表达情况及其临床意义进行探讨，旨在为临床诊治乳腺癌提供参考依据，现报道如下。

1 资料与方法

1.1 一般资料

选取 2012 年 1 月 -2017 年 8 月期间鄂东医疗集团黄石市中心医院乳甲外科的 DCIS 石蜡包埋标本（DCIS 组）59 例，IDC 石蜡包埋标本（IDC 组）32 例，乳腺癌标本纳入标准：（1）在手术前均未接受过任何治疗；（2）临床资料完整；（3）对本研究知情同意，并签署知情同意书。排除标准：（1）伴有其他恶性肿瘤者；（2）伴有免疫性疾病者；（3）伴有传染性疾病者。DCIS 组患者年龄 34-68 岁，平均（51.32± 4.16）岁，病灶直径 0.3-4.4 cm，平均（1.43± 0.54）cm，临床分期：Ⅰ期 20 例、Ⅱ期 29 例、Ⅲ期 10 例，淋巴结转移 32 例，未转移 27 例；IDC 组患者年龄 36-71 岁，平均年龄（53.71± 5.12）岁，病灶直径 0.2-4.8 cm，平均（1.52± 0.61）cm，临床分期：Ⅰ期 12 例、Ⅱ期 14 例、Ⅲ期 6 例，淋巴结转移 20 例，未转移 12 例。另选取同时期正常乳腺组织标本 20 例为对照组，年龄为 33-70 岁，平均年龄（54.36± 5.88）岁。三组年龄等一般资料对比无统计学差异（P>0.05），均衡可比，本研究通过鄂东医疗集团黄石市中心医院伦理委员会批准。

1.2 方法

将全部石蜡包埋标本制成 3 个组织芯片，切至 4 μm，进行免疫组织化学染色，应用免疫组织化学法检测 MMP-7、VEGF 及 E-cad 在三组的表达情况，MMP-7 单克隆抗体（兔抗人）工作液浓度为 1∶100，VEGF 单克隆抗体（兔抗人）工作液浓度为 1∶100，E-cad 单克隆抗体（鼠抗人）工作液浓度为 1∶100，二氨基联苯胺（DAB）试剂盒、S-P 试剂盒均由福州迈新生物试剂公司提供，所有操作均严格按照试剂盒说明进行。

1.3 阳性判断标准

阳性表达标准：MMP-7 与 VEGF 的细胞浆均匀染有棕黄色颗粒或者染有棕色，且染色强度高于背景。每张切片随机选 5 个不同位置的高倍镜视野，每个位置计数 100 个肿瘤细胞，对阳性表达的肿瘤细胞所占的比例进行计算，按照细胞浆着色深浅及阳性细胞所占比例进行阳性判断：（1）按细胞着色深浅评分：阴性记为 0 分；浅黄色记为 1 分；棕黄色记为 2 分；棕褐色记为 3 分。（2）按阳性细胞数占总细胞数的百分比进行评分：0-30%为 1 分，30%-70%为 2 分，70%-100%为 3 分。2 项评分的乘积大于或等于 3 分记为阳性（+），否则为阴性（-）。E-cad 蛋白阳性定位于细胞膜 / 细胞浆棕染，阳性判断标准同上。阳性表达率 = 阳性例数 / 总例数× 100%。

1.4 观察指标

应用免疫组织化学法检测各组 MMP-7、VEGF 及 E-cad 的表达情况，分析 MMP-7、VEGF 及 E-cad 的表达与 DCIS、IDC 患者临床病理特征的关系，并采用 Pearson 相关性分析 MMP-7、VEGF 与 E-cad 之间的相关性。

1.5 统计学方法

采用 SPSS19.0 统计学软件，计数资料以率（%）的形式表示，进行 x^2 检验，相关性分析采用 Pearson 相关性分析，以 P<0.05 为差异有统计学意义。

2 结果

2.1 各组 MMP-7、VEGF、E-cad 的表达情况比较

DCIS 组、IDC 组的 MMP-7、VEGF 阳性表达率高于对照组，E-cad 的强阳性表达率低于对照组（P<0.05），DCIS 组与 IDC 组之间的 MMP-7、VEGF、E-cad 阳性表达率比较差异无统计学意义（P>0.05），见表 1。

2.2 MMP-7、VEGF 及 E-cad 的阳性表达率与 DCIS、IDC 患者临床病理特征的关系

MMP-7、VEGF 及 E-cad 的阳性表达率均与患者的年龄、肿瘤大小无关（P>0.05），临床分期为 II-III 期、中 / 低分化程度、有淋巴结转移患者的 MMP-7、VEGF 的阳性表达率高于临床分期为 I 期、高分化程度、无淋巴结转移患者（P<0.05），中 / 低分化程度、有淋巴结转移患者的 E-cad 的阳性表达率低于高分化程度、无淋巴结转移患者（P<0.05），见表 2。

表 1 各组 MMP-7、VEGF、E-cad 的表达情况比较[n(%)]

Table 1 Comparison of the expression of MMP-7, VEGF and E-cad in each group[n(%)]

Groups	n	MMP-7		VEGF		E-cad	
		+	-	+	-	+	-
DCIS group	59	9(15.26)*	50(84.74)*	5(8.47)*	54(91.53)*	7(11.86)*	52(88.14)*
IDC group	32	5(15.62)*	27(84.38)*	4(12.50)*	28(87.50)*	6(18.75)*	26(81.25)*
Control group	20	9(45.00)	11(55.00)	11(55.00)	9(45.00)	0(0.00)	20(100.00)

Note: compared with the control group, *P<0.05.

表 2 MMP-7、VEGF 及 E-cad 的阳性表达率与 DCIS、IDC 患者临床病理特征的关系[n(%)]

Table 2 Relationship between positive expression of MMP-7, VEGF, E-cad and clinicopathological features of patients with DCIS and IDC[n(%)]

Factors		n	MMP-7	x^2	P	VEGF	x^2	P	E-cad	x^2	P
Age(years)	<50	34	26(76.47)	2.235	0.119	28(82.35)	2.547	0.112	27(79.41)	0.874	0.327
	≥ 50	57	51(89.47)			54(94.74)			51(89.47)		
Tumor size(cm)	<2cm	33	28(90.85)	0.612	0.647	27(81.82)	0.595	0.428	29(87.88)	3.215	0.06
	≥ 2cm	58	49(84.48)			54(93.10)			49(84.48)		
Clinical stages	Istage	32	23(71.88)	6.154	0.018	24(75.00)	6.017	0.014	26(81.25)	0.932	0.387
	II-IIIstage	59	54(91.53)			58(98.31)			42(71.19)		
Differenti-ation	High	49	36(73.47)	5.913	0.025	42(85.71)	7.984	0.013	45(91.84)	8.638	0.010
	Medium / low	42	41(97.62)			40(95.24)			32(76.19)		
Lymphatic metastasis	Yes	52	47(90.38)	4.497	0.032	49(94.23)	9.872	0.002	42(80.77)	6.923	0.016
	No	39	30(76.92)			33(84.62)			36(92.31)		

2.3 MMP-7、VEGF 与 E-cad 的相关性分析

经 Pearson 相关性分析显示，MMP-7 与 VEGF 存在正相关关系（r=0.362，P=0.038），MMP-7、VEGF 均与 E-cad 无显著相关性（r=0.071、0.024，P=0.057、0.089）。

3 讨论

肿瘤转移是一个多步骤完成、多基因参与的复杂过程，且受肿瘤转移相关基因的调控[12,13]。肿瘤生长主要依靠血管的生成，血管抑制因子与生成刺激因子之间的平衡是肿瘤由静止状态进展到浸润状态的关键环节，VEGF 是一种促血管生长因子，能够促进肿瘤生成新的血管，促进乳腺癌的转移和浸润[14-16]。MMP-7 是基质降解的执行酶，可降解蛋白多糖、弹力纤维、纤维连接素等，在机体内参与血管新生、炎症反应及肿瘤转移等生物学行为，有研究显示 MMP-7 表达的增加与肿瘤的浸润及转移存在相关性[17-19]。肿瘤转移与浸润的重要环节为肿瘤细胞在原发病灶上脱落，在钙粘连素细胞受体的家族中，E-cad 可增加上皮细胞紧密黏附，进而维持肿瘤组织结构的完整性，E-cad 表达的降低，则会使肿瘤细胞没有控制性的生长，并向远处转移或向周围组织侵袭[20-22]。

本研究结果显示，DCIS 组、IDC 组的 MMP-7、VEGF 阳性表达率高于对照组，E-cad 的强阳性表达率低于对照组（P<0.05），且 MMP-7、VEGF 及 E-cad 的阳性表达率均与患者的年龄、肿瘤大小无关（P>0.05），临床分期为 II-III 期、中 / 低分化程度、有淋巴结转移患者的 MMP-7、VEGF 的阳性表达率高于临床分期为 I 期、高分化程度、无淋巴结转移患者（P<0.05），中 / 低分化程度、有淋巴结转移患者的 E-cad 的阳性表达率低于高分化程度、无淋巴结转移患者（P<0.05）。说明 MMP-7、VEGF 在 DCIS 及 IDC 乳腺组织中的表达高于正常乳腺组织，且随着乳腺癌分化程度升高而降低，随着淋巴结转移而升高，分析其原因主要是因为肿瘤细胞为了进一步生长，能够分泌高水平的 VEGF，使内皮细胞迁移、增殖，并诱导新血管的形成，促进肿瘤基质形成、肿瘤持续生长及肿瘤细胞进入新生的血管最终使肿瘤发生转移 [23,24]。MMP-7 的升高主要与肿瘤的浸润与转移有关，通过降解基底膜中的层粘连蛋白和纤维连接蛋白，使肿瘤细胞可顺利突破基底膜屏障，进而协助肿瘤细胞向周围组织转移及浸润，因此其在 DCIS 及 IDC 中的阳性表达水平升高[25,26]。E-cad 在 DCIS 及 IDC 中的表达水平降低主要是因为肿瘤细胞可以通过基因突变、表达减弱、异常生化修饰、链蛋白异常或删除等多种途径来损伤 E-cad 的黏附功能[27,28]，使肿瘤细胞易于脱离原发病灶，进而发生转移与浸润，因此 DCIS 及 IDC 乳腺组织中的 E-cad 阳性表达水平低于正常乳腺组织。在对 MMP-7、VEGF 与 E-cad 相关性分析中显示，MMP-7 与 VEGF 呈显著正相关（P<0.05），MMP-7、VEGF 与 E-cad 均无相关性（P>0.05），说明 MMP-7 与 VEGF 在肿瘤血管的生成及浸润转移过程中均发挥重要作用，MMP-7 可与 VEGF 的受体结合，促进 VEGF 释放，进而促进血管的生成，同时 MMP-7 可促进细胞膜上配体降解，间接的增加肿瘤细胞分泌 VEGF，因此 MMP-7、VEGF 可能会共同促进恶性肿瘤血管的形成及肿瘤向远处侵袭转移[29,30]。

综上所述，DCIS 和 IDC 中 MMP-7、VEGF 表达高于正常乳腺组织，E-cad 表达低于正常组织，MMP-7、VEGF、E-cad 均可能参与了乳腺癌的发生及发展，在临床诊治乳腺癌患者时，可通过检测 MMP-7、VEGF、E-cad 来评估乳腺癌患者的预后，并能为乳腺癌患者的靶向治疗开辟新的方向。

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