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SDF-1 在乳腺癌患者血清中表达水平及临床意义 *

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摘要 目的: 分析 SDF-1 在乳腺癌患者外周血中的表达水平，探讨其临床意义。**方法:**Elisa 法检测乳腺癌患者术前及术后血清 SDF-1 水平,分析其与乳腺癌临床病理特征的关系。**结果:**乳腺癌患者术前(69 例)血清 SDF-1 水平明显高于正常对照组(20 例)(6406.7± 1302.5 pg/mL vs 5217.4± 1225.7 pg/mL),有明显统计学差异(P<0.01),发生远处转移的乳腺癌患者(11 例)血清 SDF-1 水平明显高于未发生转移者(58 例)(7656.4± 784.1 pg/mL vs 6169.7± 1364.6 pg/mL),差异具有明显统计学意义(P<0.01)。ER 及 Her-2 表达阳性乳腺癌的患者 SDF-1 水平较 ER 及 Her-2 表达阴性者低,差异亦有统计学意义(P<0.05)。**结论:**SDF-1 可能是预测乳腺癌发生及远处转移的重要标志物。

关键词:乳腺癌;Elisa;SDF-1;远处转移

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Serum Levels of SDF-1 in Breast Cancer and its Clinical Significance*

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ABSTRACT Objective: This study was conducted to investigate the value of the pretreatment circulating stromal cell derived factor-1 (SDF-1) in patients with breast carcinoma. **Methods:** We measured SDF-1serum concentrations and evaluated the relationship between serum SDF-1 and clinical factors in preoperative and postoperative breast cancer patients. **Results:** Serum levels of SDF-1 is higher in breast cancer patients than in controls (P <0.01), Serum levels of SDF-1 is higher in metastatic patients than non-metastatic patients (P <0.01). Serum levels of SDF-1 is higher in ER and Her-2 positive breast cancer patients than ER and Her-2 negative patients (P <0.05). **Conclusion:** SDF-1 might serve as a possible marker predicting development or distant metastasis in breast cancer.

Key words: Breast Cancer; Elisa; SDF-1; Distant metastasis

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前言

乳腺癌是常见的恶性肿瘤之一,近年来,其发病率逐年上升,已成为女性恶性肿瘤发病率第一位,虽然其诊断及治疗水平得到了很大提高,其死亡率较前有所降低,但是每年死于乳腺癌患者仍较高(5.86/10 万),术后肿瘤复发及远处转移是导致治疗失败的主要原因。研究表明，基质细胞衍生因子(stromal cell-derived factor-1,SDF-1)及其特异性受体(chemokine receptor 4,CXCR4)在肿瘤侵袭转移中起重要作用,其对免疫细胞有趋化作用，SDF-1 表达广泛,SDF-1/CXCR4 生物轴不仅是人体正常生长发育之需要,也是肿瘤侵袭和转移的重要条件[1-4]。多项研究表明 SDF-1 在肿瘤的原发及转移灶均有表达,原发灶 CXCR4 的表达高于转移灶及淋巴结，而 SDF-1 则相反，表达 SDF-1 的肿瘤细胞可能在 SDF-1 趋化牵引下,顺浓度梯度转移至作为配体产生源的某些器官,形成器官特异性的转移[1,4-8]。在对胃癌、结肠癌及骨肉瘤的研究中发现 SDF-1 与肿瘤的生长及转移关系密切,且可以预测肿瘤的转移[9-12]。那么在乳腺癌患者中是否也是如此呢？因此,本研究通过检测乳腺癌患者血清中 SDF-1 的表达,分析其与乳腺癌临床特征之间的关系,以期为乳腺癌的临床诊疗、预后评估等提供参考依据。

1 材料与方法

1.1 研究对象

选取 2011 年 6 月 -2013 年 6 月就诊于上海交通大学医学院附属新华医院(崇明),经粗针穿刺活检病理确认的乳腺癌者共 69 例为实验组,其中男 2 例,女 67 例;年龄 35～79 岁,中位年龄 53 岁。按 AJCC-TNM 分期:Ⅰ期 4 例,Ⅱ期 26 例,Ⅲ期 28 例,Ⅳ期 11 例(6 例发生肺转移,3 例发生肝脏转移,2 例发生骨转移),所有实验者就诊前均未采用放化疗。根据乳腺癌患者的肿瘤分期及患者的个人意愿选择(乳腺癌改良根治术,全乳房切除术)，手术后根据 2011 年版 NCCN 乳腺癌指南进行化疗、放疗、内分泌治疗。20 例健康志愿者为对照组。健康志愿者

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选择标准：年龄与实验者匹配，无重大疾病史、体格检查与常规生化检查均无明显异常。所有参与者均签署志愿书，并经医院伦理委员会审核。

1.2 方法

取乳腺癌患者术前、术后 1 周与术后三周及对照人群外周血 2 mL 置于含 EDTA 抗凝管中，3000 转 / 分 4 ℃离心 5 分钟，吸取上清液 500 μL 置于 -70 ℃冰箱至检测。依 Elisa 操作试剂盒（R&D systems）步骤检测血清中 SDF-1 水平，具体如下：a.加样：取待检样品 100 μL 于已包被之反应孔中，置 37 ℃ 孵育 1 小时，洗涤，（同时做空白孔，阴性对照孔及阳性对照孔）。b.加酶标抗体：于各反应孔中，加入新稀释的酶标抗体（经滴定后的稀释度）100 μL。37 ℃ 孵育 1 小时后洗涤。c.加底物液显色：加入临时配制的四甲基联苯胺(TMB)底物溶液 200 μL 于各反应孔中，37 ℃孵育 30 分钟。d.终止反应：分别加入硫酸 50 μL于各反应孔中。在（BIO RAD 公司，1420 multilabel counter）酶标仪 450 nm 光源下检测。

1.3 统计学方法

应用 SPSS15.0 软件行统计学分析，计量数据以 $\bar{x}\pm s$ 表示。两两比较经方差齐性检验后进行单因素方差分析，方差不齐数据采用秩和检验；两组间比较采用 t 检验，三组及三组以上比较应用 Kruskall-Wallis 检验，以 $P<0.05$ 表示差异有统计学意义。

2 结果

血清 SDF-1 水平：乳腺癌患者（n=69）（6406.7± 1302.5 pg/mL; 2800.5~9574.6 pg/mL）明显高于正常对照组（n=20）（5217.4± 1225.7 pg/mL；4016.9~6712.1 pg/mL）（P<0.01），发生远处转移乳腺癌患者（n=11）（7656.4 ± 784.1 pg/mL；4971.3~9574.6 pg/mL）明显高于未发生转移的患者（n=58）（6169.7± 1364.6 pg/mL；2800.5~8531.4 pg/mL）（P<0.01），未发生远处转移者亦高于正常对照组（P<0.05）（见表 1 及图 1）。SDF-1 的表达与肿瘤分期有显著相关性（P<0.01），SDF-1 的表达水平与肿瘤分期呈正比，随着肿瘤的分期的增加，SDF-1 的表达逐渐增加，发生远处转移的患者，SDF-1 浓度高达 7656.4± 784.1 pg/mL。SDF-1 的表达与年龄无明显相关（见表 1），SDF-1 水平与肿瘤病理分型，肿瘤大小、淋巴结转移亦无明显相关性；而术前及术后三周肿瘤组织表达 ER 阳性的患者 SDF-1 浓度显著高于 ER 阴性的患者，术前（6707.6± 1505.7pg/mL VS 5749.2± 1205.4 pg/mL P=0.021），术后三周（5951.7± 1459.3 pg/mL VS 5025.9± 1046.5 pg/mL，P=0.025），术后三周 Her-2 阳性患者的 SDF-1 浓度显著高于 Her-2 阴性的患者（6167.7± 1146.5 pg/mL VS 5352.4± 1359.7 pg/mL P=0.047）。术后一周 SDF-1 浓度及术后三周 SDF-1 浓度与术前比较均无显著差异性，但有先升后降的抛物线趋势（6365.4 ± 1315.6 pg/mL，7060.9± 1415.5 pg/mL，5620.1± 1342.7 pg/mL）。

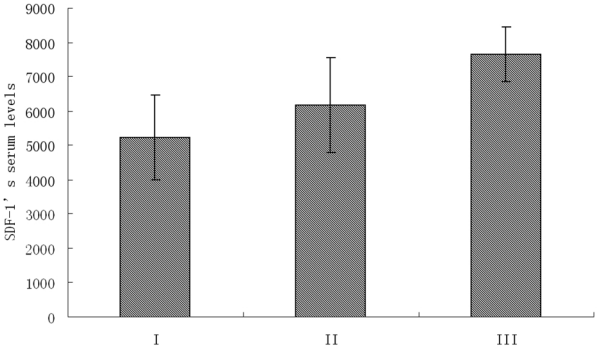

图 1 术前各组乳腺癌患者血清中 SDF-1 表达水平的比较

Fig. 1 Comparison of SDF-1's serum levels of among different group before operation

注：P<0.01，I：正常对照组；II：未发生远处转移乳腺癌患者；III：发生远处转移乳腺癌患者。

Notes: P<0.01, I: Normal control group; II: No distant metastasis in breast cancer patients; III: Distant metastasis in breast cancer patients.

表 1 术前乳腺癌患者血清 SDF-1 浓度与临床特征的关系

Table 1 The relationships between clinical features and SDF-1's serum levels of breast cancer before operation

Charactoristics	n	SDF-1's levels（pg/mL）	P
Age(years)			
≤ 53	35	6626.4± 1284.2	0.207
>53	34	6180.6± 1161.5	
Gender			
Man	2	6728.5± 506.3	
Woman	67	6397.1± 1322.7	
Stage			
Ⅰ	4	5318.6± 451.2	＜0.001
Ⅱ	26	5610.2± 1315.1	
Ⅲ	28	6810.9± 1127.0	
Ⅳ	11	7656.4± 784.1	
Distant metastasis			
present	11	7656.4± 784.1	＜0.001
absent	58	6169.7± 1364.6	
Average concentration	69	6406.7± 1302.5	

表 2 乳腺癌患者手术前后血清 SDF-1 浓度与临床病理特征的关系

Table 2 The relationships between clinical features and SDF-1's serum levels of breast cancer before and after operation

Charactoristics	n	SDF-1's levels Preoprerative	P	SDF-1's levels Postoprerative(2W)	P	SDF-1's levels Postoprerative(3W)	P
Age(years)							
≤ 53	36	6626.4± 1284.2	0.184	7129.6± 1426.4	0.802	5627.4± 1284.0	0.873
>53	31	6079.9± 1325.1		6985.8± 1341.6		5612.1± 1318.4	
Tumor diameter							
2 cm	28	6283.6± 1224.3	0.486	7086.4± 1412.8	0.423	5725.3± 1651.3	0.663
>2 cm, ≤ 5 cm	32	6352.7± 1356.8		6908.6± 1607.1		5628.1± 1322.1	
>5 cm	7	6750.7± 941.6		7655.1± 1322.1		5962.7± 1251.7	
Distant metastasis							
M0	9	7626.1± 792.6	0.001	6946.4± 842.7	0.747	5811.7± 781.4	0.566
M1	58	6169.7± 1373.1		7078.7± 1271.4		5590.4± 1374.3	
Cell type							
NIC	8	6388.5± 629.7	0.437	7303.4± 724.1	0.511	5667.8± 761.2	0.895
EIC	53	6307.8± 1151.1		6953.3± 1421.5		5608.1± 1524.5	
OIC	6	6843.4± 860.6		7688.0± 719.6		5662.5± 669.0	
Lymph node metastasis							
N0	46	6574.0± 1208.4	0.224	7264.3± 1344.2	0.176	5468.2± 1246.7	0.251
N1-3	21	5908.3± 1337.2		6615.4± 1328.6		5952.8± 1442.6	
ER							
Present	24	6707.6± 1505.7	0.021	6901.6± 1151.6	0.715	5951.7± 1459.3	0.025
Absent	43	5749.2± 1205.4		7149.8± 1604.8		5025.9± 1046.5	
PR							
Present	35	6641.2± 1085.6	0.180	7152.6± 1427.6	0.684	5733.7± 1506.6	0.428
Absent	32	6063.7± 1475.5		6960.6± 1348.5		5495.9± 1129.2	
Her-2							
Present	22	5852.2± 1286.1	0.061	7201.6± 1451.0	0.691	6167.7± 1146.5	0.047
Absent	45	6616.3± 1415.6		6992.1± 1263.1		5352.4± 1359.7	
Average concentration		6365.4 ± 1315.6		7060.9± 1415.5		5620.1± 1342.7	

NIC=Non-invasive carcinoma, EIC=Early invasive carcinoma, OIC=Other invasive carcinoma.

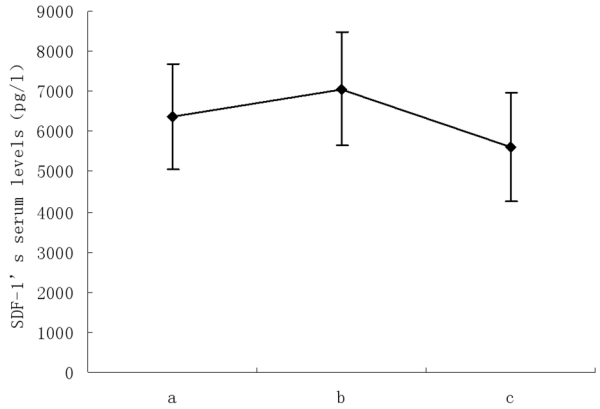

图 2 手术前后乳腺癌患者血清中 SDF-1 表达水平变化

Fig. 2 Changes of SDF-1's serum levels of breast cancer before and after operation

Note: a. Preoprerative b. Postoprerative after two weeks c. Postoprerative after three weeks.

3 讨论

乳腺癌细胞的生长转移与微环境有关,而基质细胞是乳腺癌细胞周围微环境的重要组成部分,乳腺癌细胞生长迅速且易突变,但基质细胞的生长却相对稳定。研究证实,基质细胞分泌的细胞因子可刺激细胞趋化,诱导肿瘤细胞扩散[1]。

SDF-1 是重要的基质细胞衍生因子,其对免疫细胞有趋化作用,其基因定位于 10 号染色体长臂。SDF-1 表达广泛,在肝、肺、脑、肾、心脏、骨、脑等器官中均有表达,SDF-1/CXCR4 生物轴不仅是人体正常生长发育之需要,也是肿瘤侵袭和转移的重要条件。SDF-1/CXCR4 可通过激活 MEK-MAPK-p42/44, PI-3K-AKT-NF-κ B 等信号通路参与不同的生物学效应[1-4]。

SDF-1 在结肠癌、胃癌、尤文肉瘤、脑胶质瘤、子宫内膜癌等恶性肿瘤的原发及转移灶亦有表达,原发灶 CXCR4 的表达高于转移灶及淋巴结,而 SDF-1 则相反,表达 SDF-1 的肿瘤细胞可能在 SDF-1 趋化牵引下,顺浓度梯度转移至作为配体产生源的某些器官,形成器官特异性的转移[1,4-8]。Woo 等[9]通过检测胃癌患者血清中 SDF-1 的表达, 显示胃癌患者血清中 SDF-1

的表达显著高于正常人,并进一步得出 SDF-1 可作为胃癌患者肿瘤转移的前兆标志物。Nikzaban M [10] 等研究显示 SDF-1/CXCR4 生物轴的表达与胃癌的分期密切相关。SDF-1 不仅可促进体外结肠癌细胞的转移,还可促进小鼠体内结肠癌转移灶的形成[11],Krook MA[12]最新研究发现,在尤文肉瘤细胞中,生长的压力如:无生长因子、低氧及生存空间限制,可以明显提高肿瘤细胞 CXCR4 的表达,后者导致肿瘤细胞沿 SDF-1 浓度梯度向其他脏器转移,以上研究证明 SDF-1 与肿瘤的生长及转移关系密切,且可以预测肿瘤的转移。

那么在乳腺癌患者中是否也是如此呢? Mukherjee D 等[13]研究发现 SDF-1 及其受体 CXCR4 在乳腺癌生长及转移过程中起重要作用,通过检测其表达可预测乳腺癌的转移。SDF-1 及其受体 CXCR4 通过促进乳腺癌的粘附,侵袭,乳腺癌细胞随 SDF-1 浓度梯度向靶器官转移[14]。Mü ller A 等[15]在乳腺癌最常见的转移部位淋巴结、肺、肝脏和骨髓中均检测到 CXCR4 高表达,且在 SDF-1 作用下,细胞间丝状肌动蛋白的表达成倍增加,而高表达的肌动蛋白聚合是形成伪足、促进转移所必需的,用抗 CXCR4 的抗体可阻断这些作用。Rhodes LV 等[16]研究发现 SDF-1/CXCR4 可以显著增加 ER 阳性乳腺癌细胞的雌激素抵抗,并使其恶性程度增加。这些研究说明 SDF-1 在乳腺癌的生长及转移过程中起重要作用。

我们的结果显示,乳腺癌患者血清中 SDF-1 表达显著高于正常人,表明 SDF-1 与乳腺癌之间可能存在着密切相关性;且远处转移者血清 SDF-1 表达水平明显高于未远处转移的患者,SDF-1 的表达随肿瘤的发生及转移逐渐升高,表明 SDF-1 与乳腺癌侵袭转移关系密切;SDF-1 表达随肿瘤分期呈递增趋势,尤其在乳腺癌Ⅲ期及Ⅳ期中表达显著升高,进一步证实 SDF-1 与乳腺癌浸润转移的相关性;乳腺癌术后一周 SDF-1 表达水平较术前有升高趋势,也许与 SDF-1 参与组织修复有关[1-3],术后三周 SDF-1 水平明显下降,组织修复基本完成,SDF-1 需求减少,表达明显下降,提示乳腺癌手术三周复查 SDF-1 更具临床意义。我们研究结果发现雌激素受体阳性表达的患者 SDF-1 表达较阴性者显著增加,而 Boudot A 等[17]研究发现,雌激素可以促进 SDF1 及其受体的表达,该研究和我们的结果具有相似性,而且大量研究认为[18]雌激素水平升高是乳腺癌的危险因素之一,因此雌激素促进了乳腺癌生长及转移,而其中的机制之一可能就是通过促进 SDF-1 的表达,因此我们应用内分泌治疗乳腺癌 ER 表达阳性的患者可以显著抑制肿瘤的复发及转移。HER-2 阳性的乳腺癌患者术后三周 SDF-1 表达显著高于阴性的患者,而 Li YM 等[19]研究发现在乳腺癌中 HER-2 可以显著提高 SDF-1 的表达,并且认为 HER-2 是通过刺激 SDF-1 的表达促进乳腺癌细胞的生长及转移,术前乳腺癌 HER-2 阳性与阴性之间比较 SDF-1 表达虽然无差异性,但是这可能与我们样本量少有关。由此可见 SDF-1 在肿瘤的生长及转移中起重要作用,而且 ER 及 HER-2 促进乳腺癌的生长及转移都是通过 SDF-1/CXCR4 信号起作用的,因此应用 SDF-1 或 CXCR4 特异性拮抗剂对治疗乳腺癌患者可能起到意想不到的效果[20]。

SDF-1 在远处转移的乳腺癌患者中表达更高,提示 SDF-1 可以作为乳腺癌发生转移的重要标志物,这对提高乳腺癌诊断,特别对乳腺癌治疗、手术难度及预后评估,具有明显的临床使用价值,同时随访乳腺癌术后患者血清中 SDF-1 的表达对评估乳腺癌患者预后也有重要意义。

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