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S100A14 在乳腺癌不同分子亚型中表达的临床病理研究*

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摘要 目的:探讨 S100 钙结合蛋白 A14(S100A14)在乳腺癌不同分子亚型中的表达及临床病理意义,为确定新的分子分型标志物提供依据。**方法:**254 例乳腺癌石蜡组织来源于 2013 年 1 月 16 日至 2014 年 5 月 22 日在中南大学湘雅医学院附属肿瘤医院暨湖南省肿瘤医院进行乳腺癌根治术的患者。应用免疫组织化学方法检测 S100A14 在乳腺癌组织中的表达,分析其 S100A14 在不同分子亚型乳腺癌组织中表达及其与患者临床病理指标间的相关性,采用 Kaplan-Meier 法分析 S100A14 蛋白表达与乳腺癌患者预后的关系。**结果:**S100A14 在 ER+/PR+/HER2+ 型、ER+/PR+/HER2- 型、ER-/PR-/HER2+ 型、ER-/PR-/HER2- 型乳腺癌四种分子亚型中的阳性表达分别为 38.5%、47.1%、75.5%、80.0%,以在 ER-/PR-/HER2- 型中表达最高,在 ER+/PR+/HER2+ 型中表达最低,四组间的阳性表达比较差异有显著统计学意义($P<0.01$);S100A14 的表达与乳腺癌患者术后肝转移呈正相关($r=0.134, P<0.05$),与 ER、PR 表达均呈负相关($r=-0.353, P<0.01$),而与 ER+/PR+/HER2+ 型、ER+/PR+/HER2- 型乳腺癌的临床病理特征无显著相关性($P>0.05$)。在 ER-/PR-/HER2+ 型乳腺癌中,有腋窝淋巴结转移组患者的 S100A14 阳性表达率明显高于无腋窝淋巴结转移组,差异有统计学意义($P<0.05$);在 ER-/PR-/HER2- 型中,S100A14 表达与术后肺转移呈负相关($r=-0.272, P=0.044$)。**结论:**S100A14 在不同分子亚型乳腺癌中表达存在差异,其表达与不同分子类型乳腺癌转移或复发有关,可能作为乳腺癌分子分型的候选标记物。

关键词:S100A14;乳腺癌;分子分型;临床病理

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Clinicopathological Study of S100A14 Expression in Different Molecular Subtype of Breast Cancer*

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ABSTRACT Objective: Expression and clinicopathological significance of S100 calcium binding protein A14 (S100A14) in different molecular subtypes of breast cancer were explored to provide reference for identifying new molecular typing markers. **Methods:** Breast cancer tissues were taken cases for radical mastectomy patients from January 16, 2013 to 22 May 2014 at the Cancer Hospital Affiliated to the Xiangya Medical College of Central South University & the Cancer Hospital of Hunan province. Using immunohistochemistry to detect the expression of S100A14 in 254 breast cancer tissues, with emphasis on differences expression of the protein in different molecular subtypes of breast carcinoma and its correlation with clinicopathological factors, Kaplan-Meier analysis was applied for the relationship between S100A14 expression and prognosis of patients with breast cancer. **Results:** The positive expression of S100A14 in four molecular subtypes of ER+/PR+/HER2+, ER+/PR+/HER2-, ER-/PR-/HER2+ and ER-/PR-/HER2- breast cancer was 38.5%, 47.1%, 75.5%, 80%, respectively. The expression of the 4 groups was the highest in the ER-/PR-/HER2- type and the lowest in the ER+/PR+/HER2+ type, and the difference between the 4 groups was significant ($\chi^2=32.997, P<0.001$). The relationship between S100A14 and clinicopathological characteristics of 254 cases of breast cancer was analyzed. The expression of S100A14 was significantly negatively correlated with the expression of ER and PR (all $r=-0.353, P<0.001$), and was significantly positively correlated with postoperative recurrence of liver metastasis with breast cancer ($r=0.134, P=0.040$). There is no significant correlation between the expression of S100A14 and the clinicopathological features of type ER+/PR+/HER2+ and ER+/PR+/HER2- type breast cancer ($P>0.05$). In ER-/PR-/HER2+ type breast cancer. The positive expression rate of S100A14 in axillary lymph node metastasis group was

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significantly higher than that without axillary lymph node metastasis group ($\chi^2=6.768$, $P=0.013$), and S100A4 expression has a negative correlation with postoperative pulmonary metastasis ($r=-0.272$, $P=0.044$). **Conclusion:** The expression of S100A14 in breast cancer with different molecular subtypes is different, and its high expression is associated with metastasis or recurrence of breast cancer with different molecular types. It may be used as a candidate marker for molecular typing of breast cancer.

Key words: S100A14; Breast cancer; molecular typing; Clinicopathology; significance

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前言

乳腺癌是异质性强的恶性肿瘤,分子分型可为乳腺癌内分泌治疗和靶向治疗方面提供重要的依据^[1,2]。根据雌激素受体(ertrogen receptor, ER)、孕激素受体(progesterone receptor, PR)、人类表皮生长因子受体2 (human epidermal growth factor receptor-2, HER2/CerbB-2)等分子受体表达不同将其分为不同亚型:Luminal A型、Luminal B型、HER2阳性型、基底样型以及其他类型乳腺癌^[3,4]。2011年,国际乳腺癌会议提出新增Ki-67作为分型指标之一,但Ki-67对乳腺癌分子分型还存在争议^[5-7]。本课题组前期通过蛋白质组学技术比较研究乳腺癌分子亚型的差异表达蛋白,发现S100钙结合蛋白A14(Protein S100-A14, S100A14)在不同乳腺癌分子亚型中表达存在差异^[8-10]。本研究将进一步检测S100A14在不同分子亚型中乳腺癌表达情况,并分析其临床病理意义,旨在为该分子作为乳腺癌分子分型的辅助指标提供参考依据。

1 材料与方法

1.1 一般情况

收集2013年1月16日至2014年5月22日在中南大学湘雅医学院附属肿瘤医院暨湖南省肿瘤医院住院进行乳腺手术的乳腺癌患者的石蜡包埋组织标本共254例,患者年龄28-74岁,中位年龄49岁,中位无瘤生存期38.5个月,基本临床病理情况见表1。

1.2 主要试剂

S100A14抗体(ab65860)为Abcam产品。柠檬酸盐抗原修复液(粉剂)(0.01 M, pH 6.0, MVS-0066), 0.01 MPBS(pH 7.2-7.4)。DAB显色试剂盒(Polymer, Kit-0015)和Elivision™ plus Polyer HRP(鼠/兔) Kit-9902免疫组化试剂盒均为福建迈新生物技术公司产品。

1.3 实验方法

石蜡切片常规脱蜡至水, 3% H₂O₂ 孵育 20 min, PBS 洗, 0.01 mol/L 枸橼酸盐缓冲液中微波处理 15 min 进行抗原修复, PBS 洗三次; 滴加封闭血清孵育 20 min, 滴加一抗(S100A14 抗体)4℃孵育过夜, 第一抗体工作浓度是 1:200, PBS 洗三次, 每次 5 min, 滴加生物素标记二抗 20 min, PBS 洗三次; 滴加辣根过氧化物酶标记的链霉素卵白素工作液 20 min。DAB 溶液显色; 自来水冲洗, 苏木素复染脱水封片, 光镜下观察。PBS 液代替一抗作阴性对照。结果判定根据细胞浆出现的棕黄色颗粒的细胞数和染色强度判定阳性表达情况。

1.4 免疫组化结果判定标准^[12,14]

① 阳性细胞阳性百分比评分标准: 0-4%的阳性细胞记为 0

表 1 254 例乳腺癌患者的基本临床病理情况

Table 1 The basic clinicopathological features of 254 cases of breast cancer patients

Patient characteristics	n(%)
Tumor diameter(d, cm)	
d≤ 2 cm	80(31.5)
2 cm<d≤ 5 cm	165(65.0)
d>5 cm	9(3.5)
Axillary lymph node metastasis	
no	118(46.5)
yes	136(53.5)
location	
Left side	121(47.6)
Right side	133(52.4)
Clinical stage	
Stage I	34(13.4)
Stage II	140(55.1)
Stage III	78(30.7)
Stge IV	2(0.8)
Histological grading	
Grade I-II	17(6.7)
Grade III	237(93.3)
ER	
Negative	108(42.5)
Positive	146(57.7)
PR	
Negative	108 (42.5)
Positive	146(57.5)
HER2	
Negative	121(42.5)
Positive	133(57.5)
Ki67	
<14%	64(25.2)
≥ 14%	190(74.8)
Menopause history	
Premenopause	153(60.2)
Postmenopause	105(39.8)

分,5-25%的阳性细胞记为1分,26-50%的阳性细胞记为2分,51-75%的阳性细胞记为3分,>75%的阳性细胞记为4分;③ 阳性细胞染色深度:无或边缘染色记为0分,阳性细胞呈浅黄色记为1分,阳性细胞呈黄色记为2分,阳性细胞呈棕褐色记为3分。总体评分标准为0分记为(-),1~4分记为(+),6和8分记为(++),9和12分记为(+++),0分为阴性,其余为阳性。

1.5 统计学方法

应用 SPSS20.0 统计软件对数据进行分析,采用 χ^2 检验检测 S100A14 与不同分子亚型患者中的临床病理特征的关系,使用 Fisher 精确检测进行校正,以 $P<0.05$ 表示差异有统计学意义。

2 结果

2.1 S100A14 在不同分子亚型乳腺癌中的表达

S100A14 主要在癌细胞的细胞膜表达,偶可在细胞浆中表达,以弱表达为主,在个别 ER+/PR+/HER2- 型和 ER-/PR-/HER2- 型中呈中等表达,见图 1。S100A14 在

ER+/PR+/HER2+ 型、ER+/PR+/HER2- 型、ER-/PR-/HER2+ 型、ER-/PR-/HER2- 型乳腺癌四种分子亚型中的阳性表达分别为 38.5%、47.1%、75.5%、80.0%,其中在 ER-/PR-/HER2- 型中表达最高,在 ER+/PR+/HER2+ 型中表达最低,4 组间的阳性表达率比较差异有显著统计学意义($\chi^2=32.997, P<0.01$),见表 2。组间的两两比较显示,ER-/PR-/HER2+ 型 S100A14 的表达高于 ER+/PR+/HER2+ 型 ($\chi^2=17.372, P<0.01$),ER-/PR-/HER2- 型 S100A14 的表达高于 ER+/PR+/HER2+ 型 ($\chi^2=22.549, P<0.01$),ER-/PR-/HER2+ 型中 S100A14 的表达高于 ER+/PR+/HER2- 型 ($\chi^2=9.979, P<0.01$),ER-/PR-/HER2- 型中 S100A14 的表达高于 ER+/PR+/HER2- 型 ($\chi^2=13.975, P<0.01$)。此外,S100A14 在 ER+/PR+/HER2- 型中的表达高于 ER+/PR+/HER2+ 型,ER-/PR-/HER2- 型表达高于 ER-/PR-/HER2+ 型,但差异无统计学意义($\chi^2=1.099, 0.320, P>0.05$)。

2.2 S100A14 表达与乳腺癌患者临床病理特征间的相关性

S100A14 阳性表达患者的 ER、PR 阳性表达率显著高于 S100A14 阴性表达患者,差异均有显著统计学意义($P<0.01$),而

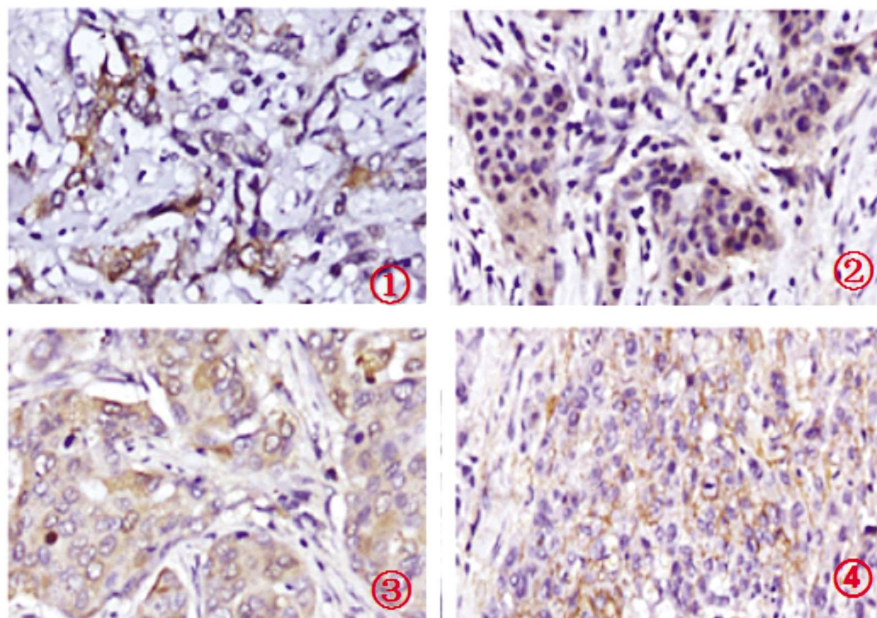


图 1 S100A14 在不同分子亚型乳腺癌中表达(HE 20×)

Fig.1 S100A14 Expression in breast cancer with different molecular subtypes

- ① S100A14 在 ER+/PR+/HER2+ 型乳腺癌中的表达 S100A14 Expression in type ER+/PR+/HER2+ breast cancer
- ② S100A14 在 ER+/PR+/HER2- 型乳腺癌中的表达 S100A14 Expression in type ER+/PR+/HER2 breast cancer
- ③ S100A14 在 ER-/PR-/HER2+ 型乳腺癌中的表达 S100A14 Expression in type ER-/PR-/HER2+ breast cancer
- ④ S100A14 在 ER-/PR-/HER2- 型乳腺癌中的表达 S100A14 Expression in type ER-/PR-/HER2- breast cancer

表 2 S100A14 在不同分子亚型乳腺癌患者中的阳性表达率比较(例,%)

Table 2 Comparison of positive expression rates of S100A14 in breast cancer patients with different molecular subtypes

S-100A14				
Subtype	Negative	Positive	χ^2	P^*
ER+PR+HER2+	48(61.5)	30(38.5)	32.997	<0.001
ER+PR+HER2-	36(52.9)	32(47.1)		
ER-PR-HER2+	13(24.5)	40(75.5)		
ER-PR-HER2-	11(20.0)	44(80.0)		

S100A14 阳性表达患者的术后肝转移率明显高于 S100A14 阴性表达患者,差异有统计学意义($P<0.05$),见表 3。S100A14 与 ER、PR(均为 $r=-0.353$, $P<0.001$)表达呈负相关。

表 3 S100A14 表达与乳腺癌患者的临床病理特征的关系(例,%)

Table 3 Relationship between S100A14 expression and clinicopathological characteristics of breast cancer patients (case,%)

Clinicopathological features	S100A14		χ^2	P
	negative (n=108)	positive (n=146)		
Age of diagnosis (age)			0.484	0.516
50<	69(63.9)	87(59.6)		
≥ 50	39(36.1)	59(40.4)		
Surgical site			1.338	0.256
L	56(51.9)	65(44.5)		
R	52(48.1)	81(55.5)		
Histological grading			0.154	0.801
grade I - II	8(7.4)	9(6.2)		
grade III	100(92.6)	137(93.8)		
Axillary lymph node metastasis			2.006	0.367
pN0	51(47.2)	67(45.9)		
pN1/2/3	57(52.8)	79(54.1)		
Tumor diameter(d, cm)			0.044	0.899
≤ 2	37(34.3)	43(29.5)		
2<d≤ 5	69(63.9)	96(65.8)		
>5	2(1.9)	7(4.8)		
clinical stages			4.305	0.283
I	18(16.7)	16(11.0)		
II	54(50.0)	86(58.9)		
III	36(33.3)	42(28.8)		
IV	0	2(1.4)		
ER			61.672	<0.01
negative	24(22.2)	84(57.5)		
positive	84(77.8)	62(42.5)		
PR			61.672	<0.01
negative	24(22.2)	84(57.5)		
positive	84(77.8)	62(42.5)		
HER2			1.917	0.204
negative	46(42.6)	75(51.4)		
positive	62(57.4)	71(48.6)		
Menstrual history			0.919	0.365
Postmenopause	39(36.1)	61(42.1)		
Premenopause	69(63.9)	84(57.9)		
Ki-67			0.418	0.561
<14%	25(23.1)	39(26.7)		
≥ 14%	83(76.9)	107(73.3)		

续表 3 S100A14 表达与乳腺癌患者的临床病理特征的关系(例,%)

Table 3 Relationship between S100A14 expression and clinicopathological characteristics of breast cancer patients (case,%)

Clinicopathological features	S100A14		χ^2	<i>P</i>
	negative (n=108)	positive (n=146)		
Relapse			0.389	0.618
yes	6(5.6)	11(7.5)		
no	102(94.4)	135(92.5)		
outcome			2.246	0.264
death	1(0.9)	3(2.0)		
no-death	112(99.1)	148(98.0)		
Postoperative lymph node metastasis			0.141	0.701
yes	3(2.8)	3(2.1)		
no	105(97.2)	143(97.9)		
bone metastasis			3.046	0.143
yes	1(0.9)	7(4.8)		
no	107(99.1)	139(95.2)		
Mediastinal metastasis			2.725	0.180
yes	2(1.8)	0		
no	111(98.2)	151(100.0)		
lung metastasis			0.724	0.576
yes	2(1.9)	1(0.7)		
no	106(98.1)	145(99.3)		
live metastasis			4.546	0.040
yes	0	6(4.1)		
no	108(100.0)	140(95.9)		
brain metastasis	1.357	0.425		
yes	1(0.9)	0		
no	107(99.1)	146(100.0)		
Chest wall or pleural metastasis			0.630	0.463
yes	4(3.7)	3(2.1)		
no	104(96.3)	143(97.9)		
Pericardial metastasis			0.724	0.576
yes	2(1.9)	1(0.7)		
no	106(98.1)	145(99.3)		
adrenal metastases			0.743	0.389
yes	0	1(0.7)		
no	108(100.0)	145(99.3)		

2.3 S100A14 表达与不同分子类型乳腺癌临床病理特征间的相关性

分析 S100A14 表达与乳腺癌四种分子亚型 ER+/PR+/HER2+ 型、ER+/PR+/HER2- 型、ER-/PR-/HER2+ 型、ER-/PR-/HER2- 型临床病理指标间的相关性,临床病理指标包

括确诊年龄、组织学分级、肿块直径、腋窝淋巴结转移、月经史、Ki-67 指数、临床分期、复发与结局状态、术后转移(淋巴结转移、骨转移、纵膈转移、肺转移、肝转移、脑转移、胸膜或胸壁转移、心包转移)等。结果显示:在 ER-/PR-/HER2+ 型乳腺癌中,有腋窝淋巴结转移者的 S100A14 表达率明显高于无腋窝淋巴结

转移者,差异有统计学意义($\chi^2=6.768, P=0.013$),而其余结果均无统计学意义。在 ER-/PR-/HER2- 型乳腺癌中, S100A14 表达与术后肺转移呈负相关($r=-0.272, P=0.044$)。

3 讨论

S100A14 是 Pietas 等在 2002 年发现的一个 S100 家族新成员,定位于人染色体 1q21,全长 cDNA 含 1067 个核苷酸,在卵巢、乳腺、子宫等肿瘤组织中过表达,在肺、前列腺、甲状腺肿瘤组织中上调,在肾脏、直肠、结肠肿瘤组织中低表达,在胃肿瘤中表达最低^[1]。本研究对不同亚型乳腺癌组织中 S100A14 表达进行检测和比较,发现 ER-/PR-/HER2- 型乳腺癌 S100A14 的阳性表达率最高,且显著高于 ER+/PR+/HER2+ 型。

S100A14 在整体及不同乳腺癌亚型中均对无瘤生存率没有显著性影响。S100A14 表达与乳腺癌亚型及术后肝转移呈正相关,与 ER、PR 表达呈负相关;在 ER-/PR-/HER2- 型中,与术后肺转移呈负相关。这与 Ehmsen 等^[2]的研究结果有部分相似性,其结果显示在三阴性乳腺癌(TNBC)中, S100A14 呈高表达,且与 TNBC 患者中尤其是 BLBC 中预后不良相关。在 S100A14 高表达乳腺癌腋窝淋巴结阴性(N⁻),与肿瘤腋窝淋巴结阳性(N⁺)的患者均显示不良预后,而 TNBC/N⁻患者则 S100A14 低表达,并且具有无瘤生存期更长。在 ER 阴性和 TNBC 患者中, S100A14 的表达与局部复发、远处扩散与脏器转移之间没有差异性。在 TNBC 和 BLBC 的患者中 S100A14 高表达的患者无瘤生存期和中位生存期明显低于的 S100A14 低表达的患者,但在 ER+、HER2+ 患者和没有表现出基底样特征的 TNBC 肿瘤患者中则没有这种现象。多因素分析显示 S100A14 是反映 TNBC 患者预后的独立因素。

有研究^[12,13]显示 S100A14 过表达可以促进细胞增殖,肿瘤发生,迁移和侵袭。S100A14 过表达增加对乳腺癌细胞顺铂为主的化疗抵抗性^[14],而这些行为可能因为 S100A14 与其它蛋白的共定位共表达相关。Tanaka 等^[15]和 Xu 等^[16]分别发现 S100A14 与 S100A16, S100A14 与 HER2 在乳腺癌内共定位于细胞膜,并且分别有其共表达。S100A14 与 S100A16 的高表达与更年轻的确诊年龄(<60 岁),ER 阴性、HER2 阳性表达状态和预后差显著相关。S100A14 与 S100A16 的单独表达均与预后较差相关,二者共表达提示肿瘤更具侵袭性及预后更差。而 S100A14 作为 HER2 信号的调控者,可与 HER2 直接结合,调控 HER2 的磷酸化,在 S100A14 沉默的乳腺癌细胞中,HER2 磷酸化和 HER2 刺激的细胞增殖降低,但是在我们的研究中并未发现 S100A14 与 HER2 之间的相关性。另一个研究^[17]显示子宫颈癌中 S100A14 过表达,并可作为作为上皮间质转换的介导因子,通过增加 N-钙粘蛋白和波形蛋白的表达并降低 E-钙粘蛋白表达,使 G2/M 期细胞的比例增加,促进细胞的增殖,迁移和侵袭。但也有报道 S100A14 在上皮样细胞中表达,而非间充质样细胞中^[12]。此外, S100A14 与卵巢癌复发有关^[18],也与肺癌在侵袭、转移和预后差有关^[19,20]。但也有报道 S100A14 可抑制转移^[21,22]。

综上所述,本研究对 S100A14 在乳腺癌不同亚型中的表达和意义进行了初步探讨,发现 S100A14 在不同分子亚型乳腺癌中表达存在差异,其表达与不同分子类型乳腺癌转移或复

发有关,可能作为乳腺癌分子分型的候选标记物,但仍需要进一步扩大病例数量和增加临床病理分析范围来明确 S100A14 的诊断价值。

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