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CD44 及 CD24 在乳腺癌组织中的表达及与临床病理特征的关系研究*

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摘要 目的: 探讨肿瘤标志因子 CD44 及 CD24 在乳腺癌组织中的表达及与临床病理特征的关系。**方法:** 选择从 2015 年 1 月到 2017 年 1 月在我院接受手术治疗的乳腺癌患者 80 例纳入本次研究,另选同期在我院治疗的导管原位癌患者 30 例,小叶增生患者 20 例及导管单纯增生患者 20 例的组织提取标本进行对照,分析 CD44 及 CD24 在乳腺癌组织和不同病变类型中的表达,并分析 CD44⁺/CD24⁺ 细胞在癌症免疫分型中的表达以及 CD44⁺/CD24⁺ 细胞与乳腺浸润导管癌相关病理特征的关系。**结果:** 乳腺癌组织内的 CD44 阳性率为 52.50%,CD24 的阳性率为 57.50%,均显著高于癌旁组织的 11.25%和 15.00%,差异均有统计学意义(均 $P < 0.05$)。CD44 及 CD24 在导管原位癌及乳腺浸润导管癌中的阳性率高于小叶增生和导管单纯增生,导管原位癌的阳性率高于乳腺浸润导管癌,差异均有统计学意义(均 $P < 0.05$),且 CD44 在乳腺浸润导管癌不同分化类型中的阳性率差异有统计学意义($P < 0.05$)。CD24 在乳腺浸润导管癌不同分化类型中的阳性率差异不显著($P > 0.05$)。CD44⁺/CD24⁺ 细胞在不同癌症免疫分型以及不同分化中的阳性率比较差异均有统计学意义($P < 0.05$)。CD44⁺/CD24⁺ 细胞与乳腺浸润导管癌患者的年龄、月经状态、肿瘤直径、淋巴结转移以及远处转移之间均无明显关系(均 $P > 0.05$)。**结论:** CD44 及 CD24 在乳腺癌组织内存在较高的阳性率,且 CD44⁺/CD24⁺ 在乳腺原位癌及低分化的乳腺癌组织内具有更高的阳性率,临床上可尝试通过监测 CD44⁺/CD24⁺ 的阳性表达情况评价患者的病情及预后。

关键词: CD44; CD24; 乳腺癌组织; 表达; 临床病理特征; 关系

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Expression of CD44 and CD24 in Breast Cancer Tissues and Their Relationship with Clinicopathological Features*

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ABSTRACT Objective: To study the expression of CD44 and CD24 in breast cancer tissues and their relationship with clinicopathological features. **Methods:** A total of 80 patients with breast cancer, who were received surgical treatment in Cangzhou People's Hospital of Hebei Province from January 2015 to January 2017, were enrolled in this study; 30 patients with ductal carcinoma in situ, 20 patients with lobular hyperplasia, 20 patients with simple ductal hyperplasia, admitted to in this hospital in the same period, were selected. Specimens were extracted from cancer patients and hyperplastic patients and compared. The expression of CD44 and CD24 in breast cancer tissues and different lesion types were analyzed, and the expression of CD44⁺/CD24⁺ cells in the cancer immune typing and the relationship between CD44⁺/CD24⁺ cells and the pathological features of breast invasive ductal carcinoma were analyzed. **Results:** The positive expression rates of CD44 and CD24 in breast cancer tissues were 52.50% and 57.50%, respectively, which were significantly higher than those (11.25% and 15.00%) in the adjacent tissues, the difference was statistically significant ($P < 0.05$). The positive rates of CD44 and CD24 in ductal carcinoma in situ and in breast invasive ductal carcinoma were higher than those in lobular hyperplasia and in simple ductal hyperplasia, the positive rate of ductal carcinoma in situ was higher than that of breast invasive ductal carcinoma, the difference was statistically significant (all $P < 0.05$). The positive rate of CD44 in different types of breast invasive ductal carcinoma was statistically significant ($P < 0.05$), and there was no significant difference in the positive rate of CD24 in different types of breast invasive ductal carcinoma ($P > 0.05$). There were significant differences in the positive rates of CD44⁺/CD24⁺ cells in different types of cancer immunology and differentiation ($P < 0.05$). There was no significant relationship between CD44⁺/CD24⁺ cells and age, menstrual status, tumor size, lymph node metastasis and distant metastasis in patients with breast invasive ductal carcinoma ($P < 0.05$). **Conclusion:** CD44 and CD24 have higher positive expression rate in breast cancer tissues, and CD44⁺/CD24⁺ has a higher positive expression rate in breast carcinoma in situ and poorly differentiated breast invasive ductal carcinoma. The patient's condition and prognosis were evaluated by monitoring the positive expression of CD44⁺/CD24⁺ in clinic.

Key words: CD44; CD24; Breast cancer; Expression; Clinicopathological features; Relationship

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前言

临床上,乳腺癌作为最为常见的一类女性恶性肿瘤,其发病率长期位居癌症的前列位置,并以每年 3% 的速度增加,而我国每年因乳腺癌死亡的患者超过了 7 万人,早期乳腺癌患者的 10 年复发率甚至高达 18.1%,对女性群体的生命安全产生了巨大的威胁^[1,2]。伴随我国工业化进程的不断加剧,我国乳腺癌的临床发病率也出现了明显的上升态势,如何更加全面地掌握和了解乳腺癌的病变机制已成为了临床上的热点课题^[3]。有报道指出,乳腺癌细胞当中含有少数存在肿瘤诱发性质的癌症干细胞,其不仅可能会促使肿瘤增殖及生长,而且对治疗药物表现出一定的耐药性,甚至将直接导致癌症治疗后的复发^[4-6]。肿瘤标志因子 CD44 处于人类基因的 11 号染色体的短臂上,其全长大约是 50kb,由 20 个保守型外显子构成,每个外显子的长度大约是 70~210bp,外显子中间则由长短各异的内含子所分开,且分布广泛的存在于细胞表面的跨膜糖蛋白,可参与到异质性黏附等过程,而此过程对于癌细胞的侵袭和转移具有促进作用^[7,8]。CD24 属于一类黏蛋白型黏附分子,也是低分子质量的高度糖基化蛋白质,其由 27 个氨基酸所构成,经由糖基磷脂酰肌醇黏附于细胞膜上,一般可在人血液系统性恶性肿瘤亦或是器官实体瘤表层发现 CD24 的高表达状态^[9]。CD44⁺/CD24⁻ 则被认为存在干细胞样和肿瘤浸润等特征,对于患者的预后影响较大^[10]。本文通过研究 CD44 及 CD24 在乳腺癌组织内的表达及与临床病理特征之间的关系,以期临床更好地治疗乳腺癌提供一定的思路及数据支持,现报道如下。

1 资料和方法

1.1 临床资料

选择从 2015 年 1 月到 2017 年 1 月在我院接受手术治疗的乳腺癌患者 80 例纳入本次研究,纳入标准:(1)初次接受乳腺手术者;(2)有手术指征;(3)患者病理学检查结果显示为乳腺浸润导管癌;(4)术前未接受其他治疗者。排除标准:(1)有其他种类的恶性肿瘤者;(2)病历资料数据缺失者;(3)有严重的心、肝、肾等脏器的功能障碍者。80 例患者均为女性,年龄 29~74 岁,平均(53.24±1.32)岁,免疫分型:LuminalA 型 25 例,B 型 13 例,HER2 过表达 15 例,基细胞亚型 27 例。分化程度:高分化 16 例,中分化 39 例,低分化 25 例。月经状态:绝经前 41 例,绝经后 39 例。肿瘤直径:<2 cm 52 例,≥2 cm 28 例。淋巴结转移:无转移 46 例,有转移 34 例。远处转移:无转移 59 例,有转移 21 例。另选同期在医院治疗的导管原位癌患者 30 例,

小叶增生患者 20 例及导管单纯增生患者 20 例的组织提取标本进行对照,本次研究已经获得了院内的伦理委员会批准。

1.2 研究方法

主要试剂:(1)鼠抗人 CD24 型单克隆抗体(SN36);(2)鼠抗人 CD44 型单克隆抗体(56-3C11);(3)鼠抗人 HER-2 型单克隆抗体(CB11);(4)SP 免疫组化涉及的单标和双标试剂盒(深圳晶美公司);(5)BCIP/NBT 碱性磷酸酯酶的显色试剂盒;(6)AEC 显色试剂盒。实验方法:将手术过程中切除的癌灶组织及癌旁正常组织各 80 例制成石蜡标本。将全部标本均予以 10% 的福尔马林固定,而后常规行石蜡包埋,选择 4 μm 的切片 4 张,再实施 HE 染色和 CD44、CD24 及 HER-2 的免疫组化染色。按照试剂盒内的说明书实施免疫组化染色步骤中的单染,分别常规给予涂片、固定、染色、水洗以及干燥等处理,染色后在显微镜下观察阳性细胞情况,而双染涉及的 CD44 通过显示黑紫色的碱性磷酸酶显色液(BCIP/NBT)显色,CD24 通过显示红色的过氧化酶显色液(AEC)显色。先进行常规脱蜡及水化,再对第一抗体进行染色,而后对第二抗体进行染色,最后在显微镜下观察阳性细胞情况。其中 CD24 和 CD44 的阳性表达评价标准如下^[11]:选择 200 个视野在 400× 的光镜下进行观察,其中阳性细胞所占比例<1%为(-),1%~10%为(+),11%~50%为(++),51%~75%为(+++),>75%为(++++)。阳性表达率=(+)例数+(++)例数+(+++)+(++++例数)/总例数×100%。通过 PBS 代替一抗用于阴性对照,再用已知的阳性乳腺癌有关切片用于阳性对照。

1.3 观察指标

分析 CD44 及 CD24 二者在乳腺癌组织内的表达,CD44 及 CD24 在不同病变类型中的表达,CD44⁺/CD24⁻ 细胞与癌症免疫分型情况,以及 CD44⁺/CD24⁻ 细胞与乳腺浸润导管癌相关病理特征的关系。

1.4 统计学方法

全部数据均通过 SPSS20.0 软件实施处理,对于计数资料以率(%)表示,比较采取确切概率法检验或者 χ^2 检验,将 $P<0.05$ 记为差异有统计学意义。

2 结果

2.1 CD44 及 CD24 在乳腺癌组织及癌旁组织内的阳性表达比较

乳腺癌组织内的 CD44 阳性表达率为 52.50%,CD24 的阳性表达率为 57.50%,均显著高于癌旁组织的 11.25% 和 15.00%,差异均有统计学意义(均 $P<0.05$),见表 1。

表 1 CD44 及 CD24 在乳腺癌组织及癌旁组织内的阳性表达比较[n(%)]

Table 1 Comparison of positive expression of CD44 and CD24 in breast cancer tissues and adjacent tissues[n(%)]

Groups	CD44		CD24	
	Positive	Negative	Positive	Negative
Breast cancer tissue(n=80)	42(52.50)	38(47.50)	46(57.50)	34(42.50)
Adjacent tissues(n=80)	9(11.25)	71(88.75)	12(15.00)	68(85.00)
χ^2	31.344	31.344	31.264	31.264
P	0.000	0.000	0.000	0.000

2.2 CD44 及 CD24 在不同病变类型中的表达

CD44 及 CD24 在导管原位癌及乳腺浸润导管癌中的阳性率均分别较小叶增生和导管单纯增生更高,且导管原位癌的阳性率较乳腺浸润导管癌也更高,差异均有统计学意义(均 $P < 0.05$)。

CD44 在乳腺浸润导管癌不同分化类型中的阳性率差异有统计学意义($\chi^2=3.168, P=0.043$)。CD24 在乳腺浸润导管癌不同分化类型中的阳性率差异不显著($\chi^2=2.898, P=0.055$),见表 2。

表 2 CD44 及 CD24 在不同病变类型中的表达[n(%)]
Table 2 Expression of CD44 and CD24 in different pathological types[n(%)]

Lesion type	n	CD44		CD24	
		Negative	Positive	Negative	Positive
Lobular hyperplasia	20	18(90.00)	2(10.00)	16(80.00)	4(20.00)
Simple ductal hyperplasia	20	17(85.00)	3(15.00)	16(80.00)	4(20.00)
Ductal carcinoma in situ	30	4(13.33)	26(86.67)* [△]	3(10.00)	27(90.00)* [△]
Invasive ductal carcinoma of breast	High differentiation	16	7(43.75)	9(56.25) [△]	9(56.25) [△]
	Middle differentiation	39	18(46.15)	21(53.85) [△]	17(43.59)
	Poorly differentiated	25	13(52.00)	12(48.00) [△]	10(40.00)

Note: Compared with invasive ductal carcinoma of breast, * $P < 0.05$;

Compared with lobular hyperplasia, [△] $P < 0.05$; Compared with simple ductal hyperplasia, [#] $P < 0.05$.

2.3 CD44⁺/CD24⁻ 细胞在不同癌症免疫分型以及不同分化的表达分析

根据免疫组化双标手段分析 CD44 及 CD24 的阳性表达结果可知,CD44⁺/CD24⁻ 在乳腺浸润导管癌中表达阳性总计有 36 例,其在 Luminal A、Luminal B、HER2 过表达及基细胞亚型

四者间的阳性率差异有统计学意义 ($\chi^2=5.941, P=0.000$), 见表 3。CD44⁺/CD24⁻ 在高分化、中分化、低分化的乳腺浸润导管癌的阳性率分别为 37.50% (6/16)、33.33% (13/39)、68.00% (17/25), 差异均有统计学意义($\chi^2=5.893, P=0.000$), 其中低分化的阳性率最高。

表 3 CD44⁺/CD24⁻ 细胞与癌症免疫分型情况的分析[n(%)]
Table 3 Analysis of CD44⁺/CD24⁻ cells and cancer immune typing[n(%)]

Immune typing	n	CD44 ⁺ /CD24 ⁻	
		Negative	Positive
Luminal A	25	17(68.00)	8(32.00)
Luminal B	13	7(53.85)	6(46.15)
HER2 overexpression	15	13(86.67)	2(13.33)
Basal cell subtype	27	7(25.93)	20(74.07)

2.4 CD44⁺/CD24⁻ 细胞与乳腺浸润导管癌相关病理特征的关系

CD44⁺/CD24⁻ 细胞与乳腺浸润导管癌患者的年龄、月经状

态、肿瘤直径、淋巴结转移以及远处转移之间均无明显关系(均 $P > 0.05$), 见表 4。

表 4 CD44⁺/CD24⁻ 细胞与乳腺浸润导管癌相关病理特征的关系[n(%)]
Table 4 Relationship between CD44⁺/CD24⁻ cells and the pathological features of breast invasive ductal carcinoma[n(%)]

Pathological features		n	Negative	Positive	χ^2	P
Age(years)	<60	47	25(53.19)	22(46.81)	0.151	0.698
	≥60	33	19(57.58)	14(42.42)		
Menstrual status	Before Menstrual	41	20(48.78)	21(51.22)	1.314	0.252
	After Menstrual	39	24(61.54)	15(38.46)		
Tumor diameter(cm)	<2	52	32(61.54)	20(38.46)	2.566	0.109
	≥2	28	12(42.86)	16(57.14)		
Lymph node metastasis	No	46	26(56.52)	20(43.48)	0.101	0.750
	Yes	34	18(52.94)	16(47.06)		
Distant metastasis	No	59	35(59.32)	24(40.68)	1.696	0.193
	Yes	21	9(42.86)	12(57.14)		

3 讨论

乳腺癌是妇女高发的肿瘤类型,对女性健康以及生命安全均造成严重威胁^[12]。经统计发现,半数以上乳腺癌患者治疗后会复发并且转移,而通过对乳腺癌患者发生复发及转移等情况分析发现,其根源在于肿瘤干细胞,并且其含量和病情严重程度以及患者预后效果等均存在一定联系^[13,14]。肿瘤干细胞主要是指肿瘤细胞范围内所存在的少部分可以诱发肿瘤的细胞,其不但有助于肿瘤快速生长,同时对临床治疗药物产生抵抗,导致患者接受化疗时,其分化细胞被迫杀死,而肿瘤细胞则得到保留,最终导致肿瘤复发^[15]。CD44 及 CD24 是肿瘤干细胞的两种表型,二者均具备诱发肿瘤功能,并且侵袭性较高,对放化疗均起到一定抵抗作用^[16]。临床认为 CD44 及 CD24 是肿瘤患者耐药的直接原因,并且其和患者复发存在必然联系^[17]。因此,有学者提出^[18,19],CD44 及 CD24 细胞所占比例较高患者出现远处转移情况的可能性更大,须予以高度重视。

本文通过研究比较后发现,乳腺癌组织内的 CD44 阳性表达率为 52.50%,CD24 的阳性表达率为 57.50%,均分别较癌旁组织的 11.25%和 15.00%明显更高,这与 Kapucuoğlu 等人^[20,21]的报道结果基本类似,提示了 CD44 及 CD24 在乳腺癌组织内均具有较高的阳性表达。原因可能是与 CD44 及 CD24 的免疫作用机制有关。具体而言,CD24 的膜糖蛋白能够介导有关细胞之间以及细胞和基质之间的黏附作用,属于 B 细胞分化的生物学标记物,对于淋巴细胞的成熟过程具有重要作用,并对癌症的产生和进展产生关键性的作用,可在多类肿瘤组织当中呈现出高表达的状态^[22,23]。CD44 属于单链的跨膜糖蛋白,并通过单基因进行编码,存在高度异质性,也是透明质酸的重要受体,其与肿瘤的进展联系紧密,主要表现在与癌细胞的增殖、浸润以及转移等情况有关,另外对于癌灶周围血管的产生也有一定的促进作用^[24,25]。因此 CD24 及 CD44 在乳腺癌组织内存在着较高的阳性表达。同时,本文发现,CD44 及 CD24 在导管原位癌及乳腺浸润导管癌中的阳性率均分别较小叶增生和导管单纯增生更高,且导管原位癌的阳性率较乳腺浸润导管癌也更高(均 $P < 0.05$),且 CD44 在乳腺浸润导管癌不同分化类型中的阳性率差异显著,但 CD24 在乳腺浸润导管癌不同分化类型中的阳性率差异不显著,这再次提示了 CD44 及 CD24 在乳腺癌中的阳性表达较良性病变更高,并且导管原位癌更高,CD44 的阳性表达与癌症的分化类型有一定关系。原因主要可能是与 CD44 及 CD24 的表达模式有关,CD24 在乳腺浸润导管癌中通常表现为胞质和胞膜均染色,其可从腔缘性的非癌组织转变成膜质性的癌组织,进而参与到肿瘤的发展过程^[26,27]。而 CD44 的阳性表达会受到癌灶的局部生长及浸润的影响,其主要依靠和细胞外基质内的透明质酸和层粘蛋白等物质的异质黏附而介导癌细胞的局部侵袭性生长。Yang 等人^[28,29]报道指出,CD44 及 CD24 均可能参与到了乳腺癌的病变过程,甚至在癌组织中达到了 50%的阳性表达率,但二者间的相互作用并不明晰。本文还发现,CD44⁺/CD24⁻ 在乳腺浸润导管癌中 Luminal A、Luminal B、HER2 过表达及基细胞亚型四者间的阳性率差异有统计学意义,在乳腺浸润导管癌分型中的表达差异有统计学意义,其中低分化的阳性率最高,为 68.00%,这与 Chen 等人^[30]的报道

类似,提示了 CD44⁺/CD24⁻ 与乳腺浸润导管癌组织内的不同免疫分型及分化程度有一定联系,但本文同时还发现 CD44⁺/CD24⁻ 细胞与乳腺浸润导管癌其他相关病理特征之间均无明显关系,这可能是因为 CD44⁺/CD24⁻ 的阳性表达参与到了基细胞型乳腺癌组织的病变过程,且会受到癌症分化程度的一定影响。而与其他病理特征之间并无明显关系则可能与研究样本量的较少有关,今后可进一步扩大样本量展开深入的研究。

综上所述,CD44 及 CD24 在乳腺癌组织内存在较高的阳性率,且 CD44⁺/CD24⁻ 在乳腺原位癌及低分化的乳腺癌组织内具有更高的阳性率,临床上可尝试通过监测 CD44⁺/CD24⁻ 的阳性表达情况评价患者的病情及预后。

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