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Kallistatin 在乳腺癌中表达的临床病理意义*

李丽萍¹ 李晶² 谭平萍³ 袁理¹ 陈凯¹ 曾亮^{1Δ}

(1 广州市妇女儿童医疗中心病理科 广东 广州 510623; 2 湖南省肿瘤医院乳腺内科 湖南 长沙 410356;

3 湖南省肿瘤医院病理科 湖南 长沙 410356)

摘要 目的:探讨 Kallistatin 在乳腺癌中表达的临床病理意义及预后价值。**方法:**收集乳腺癌档案蜡块及临床资料,分为无淋巴结转移的原发灶(NMBT),有淋巴结转移的原发灶(PBT)及配对的淋巴结转移灶(PMLN),应用免疫组化技术检测 Kallistatin 表达,统计学分析。**结果:**结果显示 kallistatin 在 PBT 组的表达高于 NMBT 组合和 PMLN 组。kallistatin 的表达与组织学类型($P=0.003$)、淋巴结状态($P<0.001$)、临床分期($P=0.002$)、雌激素受体(ER)表达($P=0.046$)有显著相关性。kallistatin 在浸润性小叶癌中的阳性表达率高于浸润性导管癌,在 PBT 组的阳性表达率显著高于 NMBT,临床分期越晚期阳性表达率越高,在 ER 阳性的病历中表达更高。Kaplan-Meier 分析显示,kallistatin 的阳性表达是乳腺癌患者无病生存时间短($P=0.008$)和总生存时间短($P=0.006$)的危险因素。在浸润性乳腺导管癌患者中,kallistatin 的阳性表达与生存时间短有关($P=0.026$)。还与 ER 阳性表达患者生存时间较短有关($P=0.010$)。**结论:**Kallistatin 在乳腺癌中的表达有较为复杂的临床病理意义,其表达提示预后不良。

关键词:激素抑制素;乳腺癌;临床病理

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Clinicopathological Significance of Kallistatin Expression in Breast Cancer*

LI Li-ping¹, LI Jing², TAN Ping-ping³, YUAN Li¹, CHEN Kai¹, ZENG Liang^{1Δ}

(1 Department of Pathology, Guangzhou Women and Children's Medical Center, Guangzhou, Guangdong, 510623, China;

2 Department of Breast Medicine, Hunan Cancer Hospital, Changsha, Hunan, 410356, China;

3 Department of Pathology, Hunan Cancer Hospital, Changsha, Hunan, 410356, China)

ABSTRACT Objective: To investigate the clinicopathological significance and prognostic value of Kallistatin expression in breast cancer. **Methods:** The wax mass and clinical data of breast cancer archives were collected and divided into primary non-lymph node metastasis (NMBT), primary lymph node metastasis (PBT) and matched lymph node metastasis (PMLN). The expression of Kallistatin was detected by immunohistochemical technique and analyzed statistically. **Results:** The results showed that the expression of kallistatin in primary lymph node metastasis was higher than that in primary lymph node metastasis without lymph node metastasis and matched lymph node metastasis. The expression of kallistatin was significantly correlated with histological type ($P=0.003$), lymph node status ($P<0.001$), clinical stage ($P=0.002$), estrogen receptor (ER) expression ($P=0.046$). The positive expression rate of kallistatin in invasive lobular carcinoma was higher than that in invasive ductal carcinoma. The positive expression rate of kallistatin in breast cancer with lymph node metastasis was significantly higher than that in breast cancer without lymph node metastasis. Kaplan-Meier analysis showed that the positive expression of kallistatin was a risk factor for short disease-free survival ($P=0.008$) and short overall survival ($P=0.006$) in breast cancer patients. In patients with invasive ductal breast cancer, the positive expression of kallistatin was associated with short survival time ($P=0.026$). It was also related to the short survival time of ER positive patients ($P=0.010$). **Conclusion:** The expression of Kallistatin in breast cancer has more complicated clinicopathological significance, and its expression suggests poor prognosis.

Key words: Kallistatin; Breast cancer; Clinicopathology

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前言

肿瘤诱导的淋巴管生成和淋巴转移是恶性肿瘤转移的常见现象。淋巴结转移情况也是肿瘤分期的重要评价指标。在乳腺癌的恶性演进过程中常常出现同侧腋窝淋巴结转移,其转移

情况影响患者的临床分期和预后。为了有针对性地阐明乳腺癌淋巴结转移的机制,本课题组应用定量蛋白质组学技术比较乳腺癌原发灶和淋巴结转移灶的差异表达蛋白,以发现在乳腺癌淋巴结转移中起关键作用的蛋白,其中发现人组织激肽释放酶结合蛋白 Kallistatin(KAL)在原发灶与淋巴结转移灶中的表达

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作者简介:李丽萍(1975-),女,主管技师,研究方向:乳腺癌及妇科肿瘤,E-mail: 18874093428@163.com

Δ 通讯作者:曾亮,主任医师,E-mail: zlxx03@126.com

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存在显著差异^[1-3]。Kallistatin/ SERPINA4 是一种丝氨酸蛋白酶抑制剂和肝素结合蛋白,属于 Serpina 家族 A 成员,被认为是一种内源性血管生成抑制剂,在抑制肿瘤生长、迁移、凋亡和炎症方面发挥着多种作用^[4-6]。但目前关于该因子与乳腺癌侵袭转移及与临床病理相关性的研究少有报道。在本研究中将重点观察该因子在乳腺癌中的表达及其临床病理意义。

1 材料与方法

1.1 临床乳腺癌石蜡组织样本

本研究共收集 161 例患者的人体石蜡包埋组织标本用于临床病理回顾性研究,其中包括 61 例无淋巴结及远处转移的乳腺癌患者,100 例有同侧腋窝淋巴结转移的乳腺癌患者。这些患者于 1996 年至 2008 年之间在中南大学湘雅医学院附属肿瘤医院/湖南省肿瘤医院行手术治疗,其基本信息总结如表 1。将对这 61 例无淋巴结及远处转移的乳腺癌(NMBT),100 例有同侧腋窝淋巴结转移的乳腺癌(PBT)和 100 例配对的淋巴结转移灶(PMLN)组织进行免疫组化检测。本研究经湖南省肿瘤医院研究伦理委员会批准,签署过知情同意书。

1.2 免疫组织化学方法

石蜡切片在 60℃ 温箱中烘烤 4 h,然后两次二甲苯中脱蜡 10 min,然后在梯度乙醇中洗涤至水。在柠檬酸抗原修复液中微波作用 15 min,并在室温下冷却。3%的过氧化氢作用 15 min。非特异性血清阻断非特异性结合后,滴加 Kallistatin 抗体(1:200,AB131053,ABCAM,UK)在 4℃ 孵育过夜。依次用生物素化二抗孵育 15 min,水洗,然后用链霉亲和素过氧化物酶结合物孵育,并用 DAB 显色。用磷酸盐缓冲液代替原抗体作为阴性对照。结果由两位高级病理医师进行独立评估,并进行比较。免疫染色总评分(TIS)是按比例评分和强度评分的乘积计算的。比例分数描述了阳性染色肿瘤细胞的估计分数(0:0-4%;1:5-25%;2:26-50%;3:51-75%;4:75%)。强度评分代表估计的染色强度(0:无染色或边缘染色;1:弱染色;2:中等染色;3:强染色)。TIS 范围从 0 到 12,设定 0 为阴性,1 及以上为阳性。

1.3 统计学方法

应用 SPSS20.0 统计软件对数据进行分析。组间比较采用卡方(χ^2)检验,配对两组间比较采用 McNemar 检验。采用 χ^2 检验检测 kallistatin 表达与 161 例乳腺癌患者的临床病理特征的关系。生存预后分析采用 Kaplan-Meier 分析并进行 log-rank 检测。 $P<0.05$ 表示差异有统计学意义。

2 结果

2.1 kallistatin 在乳腺癌组织中的表达

乳腺癌组织石蜡切片进行免疫组化染色以观察 Kallistatin 在无淋巴结转移原发灶(NMBT),有淋巴结转移的原发灶(PBT),配对的淋巴结转移(PMLN)灶。Kallistatin 染色主要见于乳腺癌细胞的胞浆(图 1A)。结果显示 kallistatin 在有淋巴结转移的原发灶中的表达高于无淋巴结转移原发灶和配对的淋巴结转移(图 1B)。

2.2 kallistatin 表达与临床病理参数的关系

kallistatin 的表达与临床表型参数之间的相关性见表 2。结果提示 kallistatin 的表达与组织学类型($P=0.003$)、淋巴结状态

($P<0.001$)、临床分期($P=0.002$)、雌激素受体(ER)表达($P=0.046$)有显著相关性。kallistatin 的表达与诊断年龄、组织学分期、肿瘤大小、孕激素受体(PR)表达、c-erbB2 及月经史无关。进一步分析 kallistatin 在浸润性小叶癌中的阳性表达率高于浸润性

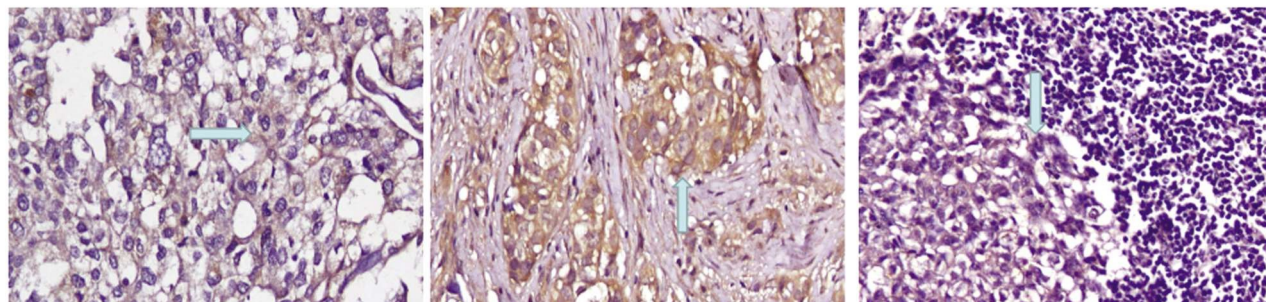
表 1 161 例乳腺癌病例的基本临床病理信息

Table 1 161 breast cancer patients basic clinicopathological information

Patient Characteristics	No. of patients
Age of diagnosis (years)	
Median age (age, range)	46(30-73)
Median survival time (month, range)	87(8-210)
Histological type, n(%)	
Ductal	128(79.5)
Lobular	33(20.49)
Histological grade, n(%)	
I-II	24(17.51)
III	137(85.09)
Nodal status, n(%)	
Negative	61(37.88)
Positive	100(62.12)
Tumor size (d, cm), n(%)	
$d \leq 2$	45(27.95)
$2 < d \leq 5$	97(60.24)
$d > 5$	18(11.18)
Unknown#	1(0.62)
Clinical stage, n(%)	
I	18(11.18)
II	85(52.79)
III	56(34.78)
IV	1(0.62)
Unknown#	1(0.62)
ER status, n(%)	
Negative	71(44.1)
Positive	90(55.9)
PR status, n(%)	
Negative	61(37.88)
Positive	100(62.12)
C-erbB-2 status, n(%)	
Negative	121(75.15)
Positive	31(19.25)
Unknown#	9(5.59)
Menstrual history, n(%)	
Premenopause	113(70.18)
Postmenopause	48(29.81)

导管癌,在有淋巴结转移的乳腺癌的阳性表达率显著高于无淋巴结转移的乳腺癌,临床分期越晚期阳性表达率越高,在 ER

A



NMBT

PBT

PMLN

B

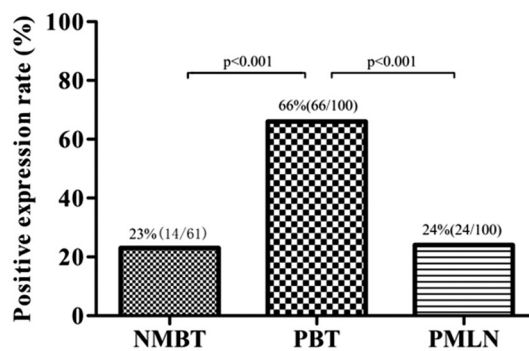


图 1 kallistatin 在乳腺癌组织中的表达

(A)kallistatin 主要在乳腺癌细胞的胞浆中表达,20×

(B)kallistatin 在乳腺癌中的阳性表达率比较

Fig.1 Expression of Kallistatin in breast cancer tissues

(A) Kallistatin was expressed in cytoplasm predominantly of breast tumor cells 20×

(B) Comparison of the positive expression rate of Kallistatin in breast Cancer tissues.

表 2 kallistatin 表达与临床病理参数的关系

Table 2 The correlation between Kallistatin expression and clinicopathological parameters

Charateristics	No. of patients	Kallistatin expression		P value*
		Negative	Positive	
Age of diagnosis (years)				0.084
<50	100	45	55	
≥ 50	61	36	25	
Histological type				0.003
Ductal	128	72	56	
Lobular	33	9	24	
Histological grade				0.394
I-II	24	14	10	
III	137	67	70	
Nodal status				0.000
Negative	61	47	14	
Positive	100	34	66	

Tumor size (d, cm)				0.120
d≤ 2	45	24	21	
2<d≤ 5	97	52	45	
d>5	18	5	13	
Unknown#	1		1	
Clinical stage				0.002
I	18	14	4	
II	85	47	38	
III	56	19	37	
IV	1	1		
Unknown#	1		1	
ER				0.046
Negative	71	42	29	
Positive	90	39	51	
PR				0.453
Negative	61	33	28	
Positive	100	48	52	
C-erbB-2				0.905
Negative	121	61	60	
Positive	31	16	15	
Unknown#	9	9		
Menstrual history				0.326
Premenopause	113	54	59	
Postmenopause	48	27	21	

* χ^2 test.

2.3 kallistatin 表达与患者生存状态的关系

Kaplan-Meier 分析显示,kallistatin 的阳性表达是乳腺癌患者无病生存时间短($P=0.008$)和总生存时间短($P=0.006$)的危险因素。进一步分析 kallistatin 表达与浸润性导管癌或 ER 阳性

患者生存状况的关系,在浸润性乳腺导管癌患者中,kallistatin 的阳性表达与生存时间短有关($P=0.026$)。此外,它还与 ER 阳性表达患者生存时间较短有关($P=0.010$),见图 2。

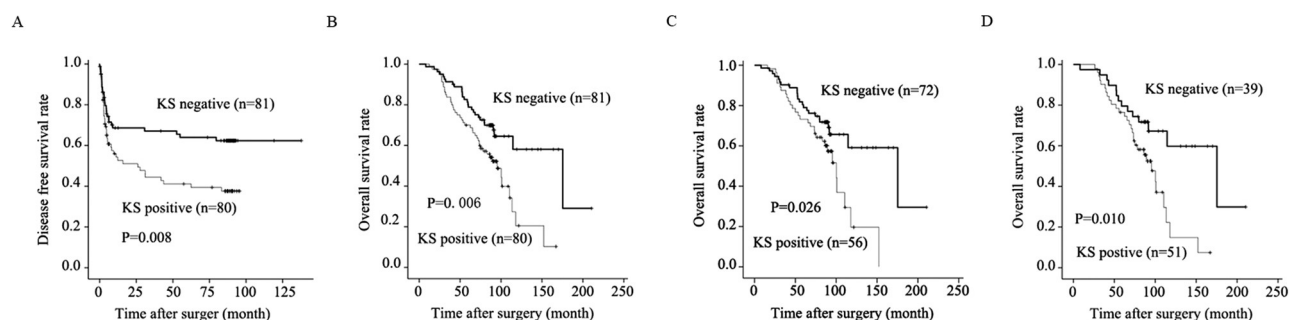


图 2 Kaplan-meier 法分析 kallistatin 表达与乳腺癌生存状态的关系

- (a) 所有乳腺癌患者 kallistatin 阴性或阳性表达病例的无病生存率
 (b) 所有乳腺癌患者 kallistatin 阴性或阳性表达病例的总生存率
 (c) 导管性乳腺癌 kallistatin 阴性或阳性表达病例的总生存率
 (d) ER 阳性表达乳腺癌 kallistatin 阴性或阳性表达病例的总生存率

Fig.2 Relation of Kallistatin expression to survival status by Kaplan-Meier method

- (A) The disease free survival rate of Kallistatin negative or positive expression of all of the breast cancer patients
 (B) The overall survival rate of Kallistatin negative or positive expression of all of the breast cancer patients
 (C) The overall survival rate of Kallistatin negative or positive expression of invasive ductal breast cancer patients
 (D) The overall survival rate of Kallistatin negative or positive expression of breast cancer patients with ER positive expression

3 讨论

本研究组前期应用 ITRAQ 蛋白组学分析乳腺癌原发灶和配对淋巴结转移灶之间的差异表达蛋白,发现 kallistatin 在乳腺癌淋巴结转移灶和原发灶存在差异表达^[1-3]。进一步在临床样本 kallistatin 在有淋巴结转移的乳腺癌原发灶中的表达高于无淋巴结转移原发灶和配对的淋巴结转移。目前关于 kallistatin 与乳腺癌关系的研究报道较少。Chao J 等发现 kallistatin 的活化位点刺激 miR-34a 和 p53 表达并抑制 miR-21-Akt-Bcl-2 信号通路,从而诱导乳腺癌凋亡^[5]。kallistatin 降低乳腺癌细胞活力、增加凋亡和 caspase-3 活性,诱导细胞自噬^[6]。kallistatin 的肝素结合位点是防止 TGF- β 诱导 mir-21 和氧化应激的关键,而其活性位点是通过与内皮表面酪氨酸激酶的相互作用刺激抗氧化基因表达的关键^[7]。而报道的 kallistatin 一个重要功能是抑制肿瘤生长和血管生成^[8],比如 kallistatin 通过抑制 NF- κ B 信号通路而抑制肿瘤血管生成^[9]。kallistatin 通过 Wnt co-receptor low-density lipoprotein receptor-related protein 6 (LRP6) 直接作用而抑制乳腺癌生长和运动^[10]。但关于乳腺癌组织中的 kallistatin 的表达及与乳腺癌临床病理指标,如亚型、临床分期等的关系尚未见报道。

本研究临床病理结果提示 kallistatin 在浸润性小叶癌中的阳性表达率高于浸润性导管癌,在有淋巴结转移的乳腺癌的阳性表达率显著高于无淋巴结转移的乳腺癌,临床分期越晚期阳性表达率越高,在 ER 阳性的病历中表达更高。本组结果说明 kallistatin 表达提示乳腺癌处于进展过程。该因子在其它恶性肿瘤中的表达有一些报道,如其表达降低与结直肠癌的浸润深度、淋巴结转移、远处转移、临床分期、肿瘤分化显著相关,也是一种独立预后因子^[17]。在胰腺癌的研究中发现 hsa_circ_0006215 和 SERPINA4 表达在胰腺癌组织中的表达较癌旁组织高^[11]。在胃癌的研究中发现 kallistatin 在胃癌组织、淋巴结转移灶表达显著下调。kallistatin 在胃癌细胞中可通过下调 VEGF-C 表达和分泌抑制淋巴血管形成和淋巴道转移^[12]。根据氧浓度的高低,氧化应激可上调或下调 kallistatin 表达^[13]。kallistatin 通过降低 ERK 和 Akt 磷酸化抑制淋巴管内皮细胞的增殖和迁移^[14]。kallistatin 抑制宫颈癌细胞增殖、迁移和上皮间质转化,并通过阻断 NF- κ B 促进凋亡^[15]。kallistatin 通过与 integrin β 3 直接作用而阻断其相关信号通路,阻止小细胞肺癌的生长和运动^[16]。这些结果反映了 kallistatin 在肿瘤发生和发展过程中作用的复杂性,在乳腺癌和胰腺癌的临床病理方面主要表现为与肿瘤进展有关,而在其它恶性肿瘤的体外实验显示出其抑制肿瘤的作用。

此外,Kaplan-Meier 生存分析提示,kallistatin 的阳性表达是乳腺癌患者无病生存时间短和总生存时间短的危险因素。进一步分层分析 kallistatin 表达与浸润性导管癌或 ER 阳性患者生存状况的关系。在浸润性乳腺导管癌患者中,kallistatin 的阳性表达与生存时间短有关,还与 ER 阳性表达患者生存时间较短有关。这些结果支持 kallistatin 阳性乳腺癌病例的生存状态差,并且与临床病理指标中 ER 表达相关性是一致的。在肝细胞肝癌中 SPTBN1 表达与 E-cadherin 和 kallistatin 水平呈正相关,SPTBN1 和 kallistatin 表达降低与无复发生存期降低有关^[18]。

本研究对 kallistatin 的临床病理研究结果与对其功能的报道有一定的不一致性,根据目前其功能研究进展可进行一定的分析,其一 kallistatin 的功能与遗传和种族有关,它在白人和黑人的子宫内膜癌间存在显著差异,部分与 PFS 显著相关。SERPINA4 是白种人表达强的一种基因,也与总生存期有关^[19],而在黑人不存在这种趋势。其二其功能与其基因结构有关,有报道 Kallistatin 通过活性位点和肝素结合区发挥作用,通过结合区抑制血管生成,也可通过活化区促进新生血管生成,其抑制或诱导细胞凋亡也依赖于细胞类型不同而不同^[20]。Kallistatin 的活化位点作用是抑制组织 kallikrein 的活性,刺激内皮一氧化氮合酶等表达与活化等,Kallistatin 的肝素结合区可拮抗 VEGF, TNF- α , Wnt, TGF- β 和 EGF 的信号通路。也有报道前列腺癌和肠癌患者血清 kallistatin 水平显著降低^[21]。这些研究报道说明影响该蛋白的因素较为复杂,在某种特定的肿瘤中其功能可能存在差异,乳腺癌作为一种异质性高的肿瘤,这种可能更为显著。

本研究较为系统地研究了 kallistatin 在乳腺癌中表达的临床病理意义,鉴于这些结果与其目前报道的部分功能不一致,将需要进一步的功能予以证实。

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