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PLK1在乳腺癌分子亚型中的表达及其与基底细胞样型乳腺癌的关系

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[摘　要]　**目的：**探讨乳腺癌各分子亚型中PLK1的表达及其与基底细胞样型乳腺癌的关系。**方法：**回顾性分析803例乳腺浸润性导管癌的临床病理资料，按照Nielsen标准将乳腺浸润性导管癌分成腺腔A型、腺腔B型、HER-2过表达型、基底细胞样型和普通乳腺样型。检测PLK1在5种不同乳腺癌亚型中的表达水平并分析其与基底细胞样型乳腺癌的关系。**结果：**PLK1在基底细胞样型、普通乳腺样型、HER-2过表达型、腺腔A型及腺腔B型乳腺癌中的阳性表达率分别为58.94%(56/95)，39.39%(65/165)，33.33%(22/66)，17.91%(79/441)及5.56%(2/36)。PLK1在ER阴性的乳腺癌分子亚型中的表达显著高于其在ER阳性的乳腺癌分子亚型中的表达，差异具有统计学意义(P<0.05)；PLK1的表达与ER呈负相关，与Ki-67表达呈正相关(P<0.01)，与HER-2无显著相关性。ER阴性乳腺癌中，PLK1在基底细胞样型乳腺癌中的阳性表达率最高，显著高于其在HER-2过表达型及普通乳腺样型乳腺癌中的表达，差异有统计学意义(P<0.05)。而HER-2过表达型与普通乳腺样型中相比，PLK1的表达差异无统计学意义(P=0.390)。PLK1的表达与基底细胞样型乳腺癌的淋巴结转移及临床分期相关，而与肿瘤大小及患者年龄无关。**结论：**PLK1过表达可能与ER阴性的基底细胞样型乳腺癌关系更密切，并在基底细胞样型乳腺的浸润、转移中起重要作用。

[关键词]　乳腺肿瘤；分子亚型；基底细胞样型；PLK1

Expression of PLK1 in molecular subtypes of breast carcinoma and its relationship with basal-like breast carcinoma

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Abstract　**Objective:** To explore the expression of PLK1 in the molecular subtypes of breast carcinoma and their relationship with basal-like breast carcinoma. **Methods:** A total of 803 cases of invasive ductal breast carcinoma were identified, the patients were subclassified in Luminal A, Luminal B, HER-2 over-expressing, basal-like and

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normal breast-like subtypes according to Nielsen criteria. The expression of PLK1 in five subtypes of invasive ductal breast carcinoma and the relationship between the expression of PLK1 and the clinicopathologic features of basal-like breast cancer were detected by immunohistochemistry. **Results:** Positive expression rate of PLK1 in basal-like, normal breast-like, HER-2 overexpressing, Luminal A, Luminal B subtypes was 58.94% (56/95), 39.39% (65/165), 33.33% (22/66), 17.91% (79/441) and 5.56% (2/36), respectively. The positive expression rate of PLK1 in ER-negative breast carcinomas (basal-like, normal breast-like and HER-2 over-expressing subtype) was significantly higher than that in ER-positive subtypes (luminal A and lumina B) (P<0.05). The expression of PLK1 was negatively correlated with ER and positively correlated with Ki-67 (P<0.01), while there was no significant correlation with the expression of PLK1 and HER-2. In cases of ER negative breast cancer, the expression of PLK1 in basal-like breast subtype was much higher than that in normal breast-like and HER-2 over-expressing subtype. The expression of PLK1 was correlated with lymph node metastasis and pTNM stage (P<0.05) of basal-like breast cancer. **Conclusion:** The overexpression of PLK1 may be closely correlated with ER-negative breast cancer, especially with basal-like breast cancer, and PLK1 may play an important role in the invasion and metastasis of basal-like breast carcinoma.

Keywords breast neoplasm; molecular subtypes; basal-like; PLK1

基于全球性基因表达分析的研究将乳腺癌分为主要的几种分子亚型，包括腺腔A型、腺腔B型、HER-2过表达型、基底细胞样型和普通乳腺样型。这些分子亚型在发病率、致病危险因素、预后、确诊时的年龄及对治疗的反应等方面都有很大区别。而基底细胞样型乳腺癌由于高发病率、缺乏有效的靶向治疗、预后差及更容易发生于年轻女性等特点而受到广泛关注[1-5]。

既往研究[6]发现基底细胞样型乳腺癌异常表达与细胞的增殖、分化及细胞周期通路相关的基因。PLK1是一种高度保守的丝/苏氨酸蛋白激酶，具有调控细胞周期、抑制肿瘤细胞凋亡和促进肿瘤形成等功能。

本研究回顾分析803例乳腺浸润性导管癌的临床病理特征，对其进行分型，并采用免疫组织化学MaxVision法检测PLK1在乳腺癌各分子亚型中的表达差异，重点探讨PLK1在基底细胞样型乳腺癌发生、发展及浸润、转移中的作用。

1 材料与方法

1.1 材料

收集2005年1月至2014年10月河北省保定市第一中心医院病理科的乳腺浸润性导管癌存档石蜡切片，选取有完整临床病理资料的803例，所有患者为女性，平均年龄51.45岁，术前均未行放疗、化疗及内分泌治疗。根据免疫组织化学结果，按照Nielsen[7]分型标准分型，ER阳性的447例，其中腺腔A型441例，腺腔B型36例。ER阴性的326例，其中HER-2过表达型66例，基底细胞样型95例，普通乳腺样型165例。本研究已通过保定市第一中心医院伦理委员会的批准。

1.2 主要试剂

兔抗人PLK1单克隆抗体均购自美国Abcam公司。即用型快捷免疫组织化学MaxVision^{TM}检测试剂盒和氨基联苯胺显色试剂盒均购自福州迈新生物生物科技有限公司。

1.3 免疫组织化学

标本经10%中性福尔马林固定、石蜡包埋、4 μm厚连续切片、免疫组织化学MaxVision两步法染色(具体操作步骤参照试剂盒说明书进行)，PBS代替一抗作为阴性对照，已知PLK1阳性的胃癌组织作为阳性对照。

1.4 结果判定

PLK1的阳性表达为棕黄色颗粒，位于细胞核和细胞质。1)染色强度，不着色为0分，呈淡黄色为1分，黄色为2分，棕褐色为3分；2)阳性染色细胞百分比0~4%为1分，5%~20%为2分，21%~40%为3分，41%~60%为4分，61%~80%为5分，81%~100%为6分，将两项评分的结果相乘，4~18分为阳性表达，0~3分为阴性表达[8]。

1.5 统计学处理

采用SPSS 23.0软件对数据进行统计学处理。计数资料采用χ^2检验，相关关系采用Spearman等级相关分析，多个样本间两两比较采用χ^2分割，α=0.05作为检验水准，P<0.05为差异有统计学意义。

2 结果

2.1 PLK1 在各型乳腺癌中的表达

ER阴性的乳腺癌亚型中，PLK1的阳性表达率显著高于ER阳性乳腺癌亚型，差异有统计学意义(P<0.005)。ER阴性的乳腺癌中，PLK1在基底细胞样型乳腺癌中的表达水平最高，HER-2过表达型与普通乳腺样型中相比，PLK1的表达差异无统计学意义(P>0.05)。ER阳性的乳腺癌中，PLK1在腺腔A型与腺腔B型中的表达差异无统计学意义(P>0.05)。PLK1的表达与ER呈显著负相关(χ^2=69.584，r=−0.294，P<0.001)，与Ki-67表达呈显著正相关(χ^2=9.296，r=0.107，P=0.002)，而与HER-2无显著相关性(χ^2=1.107，P=0.239；表1，图1)。

2.2 PLK1 与基底细胞样乳腺癌临床病理特征的关系

PLK1的表达与基底细胞样乳腺癌淋巴结转移及pTNM分期密切相关(P<0.001)，与肿瘤大小及患者年龄无关(表2)。

表1 PLK1蛋白在各乳腺癌亚型中的表达

Table 1 Expression of PLK1 in each subtype of breast carcinoma

类别	n	PLK1/[例(%)]		χ^2	P
		+	−		
乳腺癌分子亚型				88.135	<0.001
管腔A型	441	79 (17.91)	362 (82.09)		
管腔B型	36	2 (5.56)	34 (94.44)		
HER-2过表达型	66	22 (33.33)*	44 (66.67)		
基底细胞样型	95	56 (58.94)$^{\&\#}$	39 (41.06)		
普通乳腺样型	165	65 (39.39)§	100 (60.61)		
ER				69.584	<0.001
+	477	81†	396		
−	326	143	183		
HER-2				1.107	0.239
+	102	24	78		
−	701	200	501		
Ki-67				9.296	0.002
高表达(>20%)	429	139‡	290		
低表达(<20%)	374	85	289		

*：与管腔A型相比，χ^2=8.556，P=0.003；与管腔B型相比，χ^2=9.989，P=0.002。$^{\&}$：与管腔A型相比，χ^2=69.844，P<0.001；与管腔B型相比，χ^2=30.164，P<0.001；与HER-2过表达型相比，χ^2=10.230，P=0.001。$^{\#}$：与基底细胞样型相比，χ^2=9.265，P=0.002。§：与管腔A型相比，χ^2=30.582，P<0.001；与管腔B型相比，χ^2=15.227，P<0.001。†：与ER表达的关系r=−0.294。‡：与Ki-67表达的关系r=0.107。

*: compared with Luminal A, χ^2=8.556, P=0.003; compared with Luminal B, χ^2=9.989, P=0.002. $^{\&}$: compared with Luminal A, χ^2=69.844, P<0.001; compared with Luminal B, χ^2=30.164, P<0.001; compared with HER-2 over-expressing, χ^2=10.230, P=0.001. $^{\#}$: compared with normal breast-like, χ^2=9.265, P=0.002. §: compared with Luminal A, χ^2=30.582, P<0.001; compared with Luminal B, χ^2=15.227, P<0.001. Correlation of PLK1 and ER: $^{\dagger}r$=−0.294; correlation of PLK1and Ki-67 index: $^{\ddagger}r$=0.107.

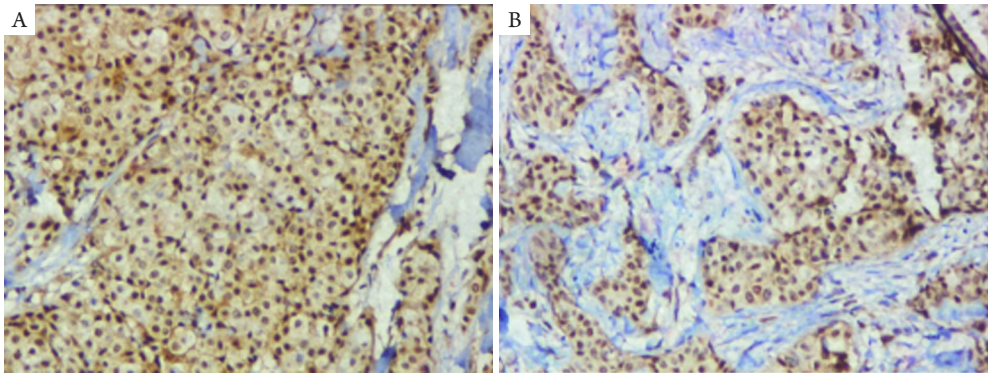

图1 PLK1在乳腺癌中的表达(IHC，×200)

Figure 1 Expression of PLK1 in breast carcinoma (IHC, × 200)

(A) PLK1在非基底细胞样型乳腺癌中的阳性表达；(B) PLK1在基底细胞样型乳腺癌中的阳性表达。

(A) Positive expression of PLK1 in non-basal-like breast carcinoma; (B) Negative expression of PLK1 in basal-like breast carcinoma.

表2 PLK1蛋白表达与基底细胞样型乳腺癌临床病理参数的关系

Table 2 Relationship between PLK1 protein expression and clinicopathological parameters of basal-like breast carcinoma

临床病理参数	*n*	PLK1		χ^2	*P*
		+	−		
年龄/岁				0.272	0.602
<50	42	26	16		
≥50	53	30	23		
肿瘤大小				3.750	0.153
T1	30	14	16		
T2	52	32	20		
T3	13	10	3		
淋巴结转移				7.424	0.006
无	38	16	22		
有	57	40	17		
TNM分期				16.256	<0.001
I~II	63	28	35		
III~IV	32	28	4		

3 讨论

PLK1是一种丝/苏氨酸蛋白激酶，在细胞周期调节中发挥着重要作用。PLK1包含有一个保守的N末端激酶催化结构域，一个参与底物连接作用的C末端polo框结构域(polo-box domain，PBD)。PLK1几乎调节细胞分裂的每个阶段，包括有丝分裂的起始、中心体成熟、双极纺锤体形成，姐妹染色单体分离、有丝分裂退出和胞质分裂[9-10]。除在有丝分裂和胞质分裂中的作用，近期研究[11-12]显示PLK1在调节微管动力学、DNA复制、染色体动力学、P53活性和G2 DNA损伤修复的调节过程中发挥重要作用。PLK1在多种肿瘤中过表达，且其表达水平与细胞高增殖率、高转移潜能和预后差有关[13-14]。

King等[8]研究发现：PLK1与ER-α的表达相

关，并与三阴性乳腺癌(triple negative breast cancer，TNBC)关系更密切。Maire等[15]研究发现：与乳腺癌的腺腔A型、腺腔B型、HER-2过表达型相比，PLK1在TNBC中表达水平更高，而且认为PLK1是TNBC潜在的治疗靶点。本研究结果发现：与ER阳性的乳腺癌分子亚型相比，PLK1在ER阴性的乳腺癌分子亚型中表达率更高，且与ER的表达呈显著负相关，与Ki-67表达呈显著正相关。结果提示：PLK1过表达可能在高增殖活性的ER阴性乳腺癌的癌变过程中发挥着更加重要的作用。

基底细胞样型乳腺癌作为一种新近发现的特殊乳腺癌分子亚型，具有独特的组织学结构和生物学行为，且目前尚无有效的靶向治疗药物，预后较差。李志峰等[16]发现PLK1高表达的乳腺癌患者组无疾病进展期及总体生存期均低于PLK1低表达的乳腺癌患者组。本研究结果显示：ER阴性乳腺癌分子亚型中，PLK1在基底细胞样型乳腺癌中的阳性表达率最高，且显著高于其他两型；同时，PLK1的表达与基底细胞样型乳腺癌的淋巴结转移及临床分期具有显著相关性，提示PLK1过表达可能与基底细胞样型乳腺癌的发生、发展关系更加密切，且PLK1的表达与基底细胞样型乳腺癌的侵袭、转移能力有关，提示PLK1可能成为评估基底细胞样型乳腺癌预后的有效指标及潜在靶点。

既往研究[17-19]发现：靶向PLK1的siRNA能够有效抑制多种恶性肿瘤的增殖，使肿瘤细胞阻滞于G_2/M期，并诱导肿瘤细胞凋亡及对放、化疗的敏感性。因此，以PLK1作为治疗靶点的抑制剂的研发可能为基底细胞样型乳腺癌的个体化治疗提供一条新的思路。

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