



DOI: 10.3969/j.issn.2095-1264.2024.05.06

文章编号: 2095-1264(2024)05-0554-06

## EPB41L3 基因甲基化参与调控宫颈癌进展的 相关性研究<sup>\*</sup>

张媛媛<sup>1</sup>, 朱江<sup>2</sup>, 赵静<sup>1</sup>, 古扎丽努尔·阿不力孜<sup>1\*</sup>, 沙丽娅·阿不都吾甫<sup>1</sup>

(<sup>1</sup>新疆医科大学附属肿瘤医院, 新疆 乌鲁木齐, 830000; <sup>2</sup>新疆医科大学第一附属医院, 新疆 乌鲁木齐, 830054)

**摘要:** **目的** 探究 EPB41L3 基因甲基化与宫颈癌进展的相关性。**方法** 收集临床慢性宫颈炎、高级别宫颈上皮内瘤变及宫颈癌患者的宫颈组织,用基因甲基化特异性 PCR 扩增(MSP)试剂盒检测样本中 EPB41L3 基因的甲基化水平;另外选取宫颈癌 HeLa 细胞和 SiHa 细胞,以人正常宫颈上皮细胞 HUCEC 作为对照,PCR 检测细胞中 EPB41L3 基因甲基化水平,RT-PCR 和免疫印迹检测 EPB41L3 基因表达水平;根据是否使用去甲基化药物 5-氮杂-2'-脱氧胞苷(5AZA)将细胞分为 4 组:HeLa+Control 组、HeLa+5AZA 组、SiHa+Control 组、SiHa+5AZA 组。采用 CCK8 实验检测各组细胞的增殖率,Transwell 实验检测各组细胞的迁移率,流式细胞术检测各组细胞的凋亡率,进行组间对比分析。**结果** 慢性宫颈炎、高级别宫颈上皮内瘤变、宫颈癌组织中 EPB41L3 甲基化百分比分别为 6.67%、73.33%、93.33%。在 HeLa 细胞和 SiHa 细胞中均检测到 EPB41L3 甲基化。EPB41L3 基因在 HeLa 细胞和 SiHa 细胞中的表达水平均显著低于对照组( $P<0.0001$ ,  $P=0.0025$ )。HeLa+5AZA 组细胞增殖率显著低于 HeLa+Control 组( $P=0.0035$ ),SiHa+5AZA 组细胞增殖率显著低于 SiHa+Control 组( $P=0.0060$ )。HeLa+5AZA 组细胞迁移率显著低于 HeLa+Control 组( $P=0.0009$ ),SiHa+5AZA 组细胞迁移率显著低于 SiHa+Control 组( $P=0.0019$ )。HeLa+5AZA 组细胞凋亡率显著高于 HeLa+Control 组( $P=0.0024$ ),SiHa+5AZA 组细胞凋亡率显著高于 SiHa+Control 组( $P=0.0024$ )。**结论** EPB41L3 基因甲基化后可能失去对宫颈癌细胞的抑制作用,其表达水平与宫颈癌进展可能呈正相关。

**关键词:** 宫颈癌; EPB41L3; 甲基化

**中图分类号:** R737.33 **文献标识码:** A

## Correlation between methylation of EPB41L3 gene and regulation of cervical cancer progression<sup>\*</sup>

ZHANG Yuanyuan<sup>1</sup>, ZHU Jiang<sup>2</sup>, ZHAO Jing<sup>1</sup>, GUZALINUR Abudzi<sup>1\*</sup>, SHALIYA Abuduwufu<sup>1</sup>

(<sup>1</sup>Cancer Hospital Affiliated to Xinjiang Medical University, Urumqi, 830000, Xinjiang, China; <sup>2</sup>The First Affiliated Hospital of Xinjiang Medical University, Urumqi, 830054, Xinjiang, China)

**Abstract: Objective** To investigate the correlation between EPB41L3 gene methylation and cervical cancer progression. **Methods** Cervical tissues of patients with clinical chronic cervicitis, cervical intraepithelial neoplasia and cervical cancer were collected. The methylation of EPB41L3 gene in the samples was detected by gene methylation-specific PCR amplification (MSP) kit. Taking the normal cervical epithelial cells as control, the methylation of EPB41L3 gene in HeLa and SiHa cervical cancer cell lines were detected by PCR. The expression levels of EPB41L3 gene in cervical cancer cell

<sup>\*</sup> 基金项目:新疆维吾尔自治区自然科学基金项目(2021D01C404);“天山英才”医药卫生高层次人才培养项目(TSYC202301B076)。

作者简介:张媛媛,女,博士,主任医师,研究方向为妇科肿瘤。

\*通信作者:古扎丽努尔·阿不力孜,女,博士,主任医师,研究方向为妇科肿瘤。

lines and normal cervical epithelial cell lines were detected by RT-PCR and western blotting. Cells were divided into four groups according to whether the demethylated drug 5-aza-2'-deoxycytidine (5AZA) was used: HeLa group, HeLa+5AZA group, SiHa group, and SiHa+5AZA group. In addition, CCK8 assay was used to detect cell proliferation rate, Transwell assay was used to detect cell mobility, flow cytometry was used to detect cell apoptosis rate in each group. Comparative analysis was performed between the groups. **Results** The methylation percentage of EPB41L3 in chronic cervicitis, cervical intraepithelial neoplasia and cervical cancer was 6.67%, 73.33% and 93.33%, respectively. EPB41L3 methylation was detected in HeLa and SiHa cells. The expression of EPB41L3 in HeLa and SiHa cells was significantly lower than that in the control group ( $P<0.0001$ ,  $P=0.0025$ ). The cell proliferation rate of HeLa+5AZA group was significantly lower than that of HeLa+Control group ( $P=0.0035$ ), and that of SiHa+5AZA group was significantly lower than that of SiHa+Control group ( $P=0.0060$ ). The cell migration rate of HeLa+5AZA group was significantly lower than that of HeLa+Control group ( $P=0.0009$ ), and that of SiHa+5AZA group was significantly lower than that of SiHa+Control group ( $P=0.0019$ ). The cell apoptosis rate of HeLa+5AZA group was significantly higher than that of HeLa+Control group ( $P=0.0024$ ), and that of SiHa+5AZA group was significantly higher than that of SiHa+Control group ( $P=0.0024$ ). **Conclusion** EPB41L3 gene may lose its inhibitory effect on cervical cancer cells after methylation, and its expression level may be positively correlated with the progression of cervical cancer.

**Key words:** Cervical cancer; EPB41L3; Methylation

## 前言

宫颈癌是女性生殖系统三大恶性肿瘤之一,每年新增病例约 50 万,其中绝大多数病例发生于发展中国家<sup>[1-2]</sup>。开展宫颈癌发病机制研究及个体化治疗方案研发,对提高宫颈癌患者生活质量、降低病死率具有重要意义。EPB41L3 是一种的重要膜骨架蛋白,在细胞黏附、运动和生长中发挥作用。越来越多的研究发现,EPB41L3 在多种肿瘤中异常表达,如在食管鳞癌、非小细胞肺癌、乳腺癌、胶质瘤、脑膜瘤等多种肿瘤中均表达下调<sup>[3-5]</sup>。Yamada 等<sup>[6]</sup>发现,EPB41L3 在肾透明细胞癌中常发生甲基化,可能成为手术切除后复发转移的独立预后指标。本课题组前期研究发现,EPB41L3 基因过表达不仅可抑制宫颈癌 HeLa 细胞和 SiHa 细胞的增殖和克隆形成能力,还可以阻滞细胞周期,促进凋亡<sup>[7]</sup>。然而,EPB41L3 在宫颈癌中的作用机制尚不完全清楚。因此,本课题组在前期研究的基础上检测宫颈癌细胞中 EPB41L3 甲基化水平,并通过去甲基化药物处理不同的宫颈癌细胞,对细胞的增殖、迁移、浸润和凋亡等进行检测,验证 EPB41L3 甲基化水平变化对宫颈癌细胞的影响,以期对宫颈癌的临床治疗提供新的策略和靶点。

## 1 材料与方法

### 1.1 细胞

宫颈癌细胞株 HeLa、SiHa 与人正常宫颈上皮细胞株 HUCEC 均购自武汉普诺赛生命科技有限

公司。

### 1.2 仪器与试剂

人脑微血管内皮细胞完全培养基(武汉普诺赛生命科技有限公司);胎牛血清(美国 Gibco 公司),胰酶(美国 Hyclone 公司);青霉素、链霉素双抗(各  $1\ 000\ 000\ \text{U}\cdot\text{L}^{-1}$ ),5%  $\text{CO}_2$  培养箱(日本 SANYO,  $\times\text{D}-101$ );超净工作台(苏州净化, SW-CJ-1FD);倒置相差显微镜(日本 OLYMPUS, B $\times$ 51);DNA 提取试剂盒(天根生化科技北京有限公司, DP304);涡旋振荡仪(海门市其林贝尔仪器制造有限公司, QL-902);离心机(Eppendorf, Centrifuge 5415D);分光光度计(Thermo Scientific, NANODROP 2000);凝胶成像系统(上海天能科技有限公司, Tanon 1600);荧光定量 PCR 仪(Applied Biosystems, ABI7500)。

### 1.3 方法

**1.3.1 目标区域甲基化水平检测** 分别取 60 例临床慢性宫颈炎、高级别宫颈上皮内瘤变及宫颈癌患者的宫颈组织进行目标区域甲基化水平检测。宫颈癌患者病理类型均为鳞癌。本研究已通过新疆医科大学附属肿瘤医院伦理委员会批准,所有标本来自新疆医科大学附属肿瘤医院,所有患者均签署知情同意书。用液氮将组织样本研磨后放入离心管中,用 DNA 提取试剂盒提取基因组,用甲基化特异性 PCR 扩增(methylation-specific PCR, MSP)试剂盒检测样本中目的基因的甲基化水平。甲基化检测引物均由北京 Invitrogen 公司合成(表 1)。

**1.3.2 RT-PCR 和免疫印迹检测细胞中 EPB41L3 的表达** 用 TRIzol 试剂盒提取 HeLa 细胞、SiHa 细

表 1 引物序列  
Tab. 1 Primer sequences

基因	引物序列
EPB41L3 (非甲基化)	F 5'-TTTGTGTATTGT TGGTGGAGGAGTG-3' R 5'-CACAAATCCCCCACTCCA AAAACA-3'
EPB41L3 (甲基化)	F 5'-GCAGTG CAAAGTGATACTTC-3' R 5'-TCTGGTGGATAAA ATTTACAT-3'

胞、HUVEC 细胞中的总 RNA,紫外吸收测定法检测 RNA 浓度和纯度,变性琼脂糖凝胶电泳,逆转录合成 cDNA,RT-PCR 检测 EPB41L3 基因表达。每个样本重复检测 3 次,数据采用  $2^{-\Delta\Delta Ct}$  法进行分析。提取细胞总蛋白,进行 SDS-聚丙烯酰胺凝胶电泳,转膜,抗体结合反应,标记物显色,图像分析软件分析目的条带灰度值,计算 EPB41L3 蛋白相对表达量。

**1.3.3 细胞分组** 用去甲基化药物 5-氮杂-2'-脱氧胞苷 (5-aza-2'-deoxycytidine, 5AZA) 处理宫颈癌 HeLa 细胞和 SiHa 细胞。药物组加入  $1 \mu\text{mol}\cdot\text{L}^{-1}$  5AZA,对照组加入相同体积的 PBS,将细胞分为 4 组: HeLa+Control 组、HeLa+5AZA 组、SiHa+Control 组、SiHa+5AZA 组。

**1.3.4 CCK8 实验检测细胞增殖** 按照上述分组对细胞进行铺板培养,置于  $37^\circ\text{C}$ 、5%  $\text{CO}_2$  温箱培养 24 h,使细胞贴壁。取对数生长期细胞接种至 96 孔板,每孔  $100 \mu\text{L}$  (10 000 个),培养 72 h。向每孔加入  $10 \mu\text{L}$  CCK8 溶液,孵育 4 h。用酶标仪测定 450 nm 处吸光度,每组设置 3 个复孔,连续检测 4 天。

**1.3.5 Transwell 实验检测细胞迁移** 按照上述分组将细胞接种至 Transwell 小室。取对数生长期细胞,弃去无血清培养基,常规胰酶消化,加入无血清培养基。离心,弃上清,加入适量无血清培养基重悬细胞。对细胞进行计数后,将一定数量的 Transwell 小室置于 24 孔板,取上述细胞悬液  $400 \mu\text{L}$  逐滴加入小室;取  $500 \mu\text{L}$  含 10% 血清的培养基沿小室侧壁与孔壁的空隙处加入孔中, $37^\circ\text{C}$ 、5%  $\text{CO}_2$  条件下常规培养 48 h,对细胞进行染色、拍照,并计算迁移率。

**1.3.6 流式细胞术检测细胞凋亡** 用不含 EDTA 的胰酶消化各组细胞, $2000 \text{ r}\cdot\text{min}^{-1}$  室温离心 5~10 min,收集细胞,洗涤 2 次,再用  $1\times$  Binding Buffer 缓冲液制成  $1\times 10^6$  个/mL 的细胞悬液,取  $300 \mu\text{L}$  加入 Falcon 试管,用 Annexin V-FITC 和 PI 进行标记,1 h 内上样,用流式细胞仪检测细胞凋亡。

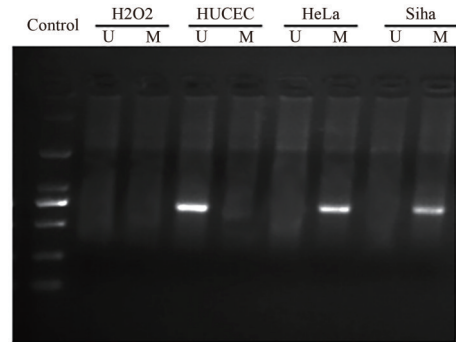
## 1.4 统计学方法

采用 GraphPad Prism 5.0 软件进行统计学分析,计量资料用“均数 $\pm$ 标准差”( $\bar{x}\pm s$ )表示,组间比较采用 *t* 检验, $P<0.05$  表示差异有统计学意义。

## 2 结果

### 2.1 目标区域甲基化水平检测

慢性宫颈炎、高级别宫颈上皮内瘤变、宫颈癌组织中 EPB41L3 甲基化百分比分别为 6.67% (4/60)、73.33% (44/60)、93.33% (56/60)。对不同宫颈癌细胞株与正常宫颈上皮细胞进行甲基化 PCR 检测,在宫颈癌 HeLa 细胞及 SiHa 细胞中检测到 EPB41L3 甲基化(图 1)。



注:M 表示 EPB41L3 基因甲基化;U 表示 EPB41L3 基因非甲基化。

Note: M represents EPB41L3 gene methylation. U represents unmethylated EPB41L3 gene.

图 1 不同宫颈癌细胞与正常宫颈上皮细胞的甲基化 PCR 检测结果

Fig. 1 Methylation PCR results of different cervical cancer cells and normal cervical epithelial cells

### 2.2 RT-PCR 和免疫印迹检测 EPB41L3 的表达

RT-PCR 和免疫印迹结果显示,EPB41L3 在 HeLa 细胞和 SiHa 细胞中的表达水平均显著低于对照组 ( $P<0.05$ ) (图 2)。

### 2.3 去甲基化对宫颈癌细胞增殖的影响

细胞经去甲基化药物 5AZA 处理后,第 1~2 天增殖率较低,第 3~4 天保持了较高的增殖率;从第 3 天开始,HeLa+5AZA 组与 HeLa+Control 组、SiHa+5AZA 组与 SiHa+Control 组增殖率有了明显差异;第 4 天,HeLa+5AZA 组细胞增殖率显著低于 HeLa+Control 组, SiHa+5AZA 组细胞增殖率显著低于 SiHa+Control 组,差异均有统计学意义 ( $P<0.05$ ) (图 3)。

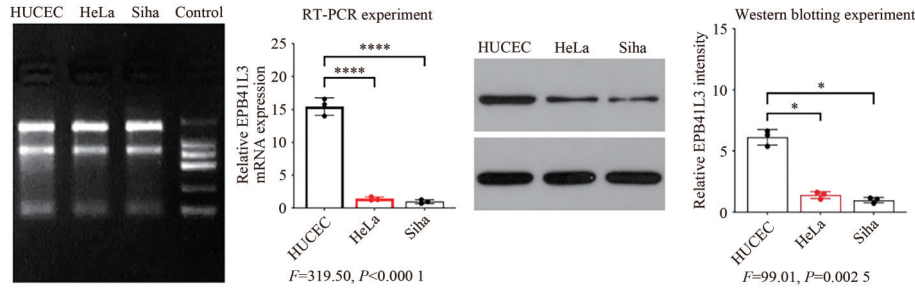


图 2 RT-PCR 和免疫印迹检测 EPB41L3 的表达

Fig. 2 EPB41L3 expression detected by RT-PCR and immunoblotting

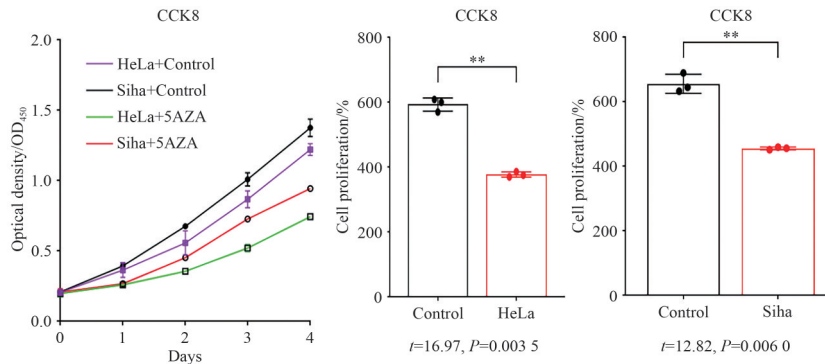


图 3 去甲基化对宫颈癌细胞增殖的影响

Fig. 3 Effect of demethylation on the proliferation of cervical cancer cells

### 2.4 去甲基化对宫颈癌细胞迁移的影响

HeLa+5AZA 组细胞迁移率显著低于 HeLa+

Control 组, Siha+5AZA 组细胞迁移率显著低于 Siha+Control 组, 差异均有统计学意义 ( $P < 0.05$ ) (图 4)。

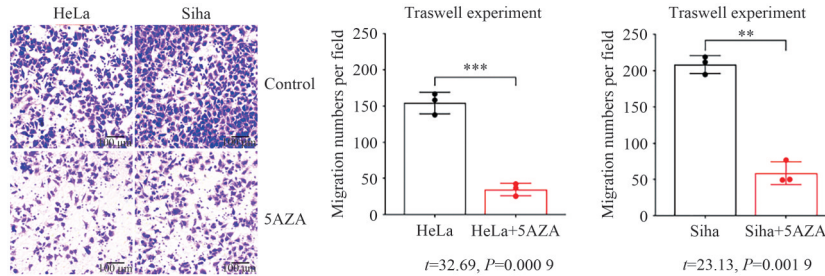


图 4 去甲基化对宫颈癌细胞迁移的影响

Fig. 4 Effect of demethylation on the migration of cervical cancer cells

### 2.5 去甲基化对宫颈癌细胞凋亡的影响

HeLa+5AZA 组细胞凋亡率显著高于 HeLa+Control 组, Siha+5AZA 组细胞凋亡率显著高于 Siha+Control 组, 差异均有统计学意义 ( $P < 0.05$ ) (图 5)。

## 3 讨论

宫颈癌属于妇科恶性肿瘤, 在亚洲地区女性肿瘤中发病率排名第二, 死亡率位居第四, 亚洲宫颈癌发病及死亡病例占全球一半以上, 而我国占比高达 30%<sup>[1-2]</sup>。宫颈癌的发生与多种因素相关, 其致病

机制尚未明确, 但与其关系最为密切的是高危型人乳头瘤病毒 (human papillomavirus, HPV) 持续感染<sup>[7]</sup>。目前, 临床主要采用手术、放疗、化疗等方法治疗宫颈癌。随着医学与多学科的交叉渗透发展, 以及患者对生存乃至生活质量的要求提高, 精准治疗也逐渐被纳入临床治疗中<sup>[8-10]</sup>。

已有研究证明, EPB41L3 基因可能在多种肿瘤中发挥抑癌作用<sup>[11-13]</sup>, EPB41L3 表达下调可导致细胞骨架组织破坏, 从而促进肿瘤细胞侵袭和迁移。有研究发现, EPB41L3 在多种肿瘤中低表达<sup>[14-18]</sup>。



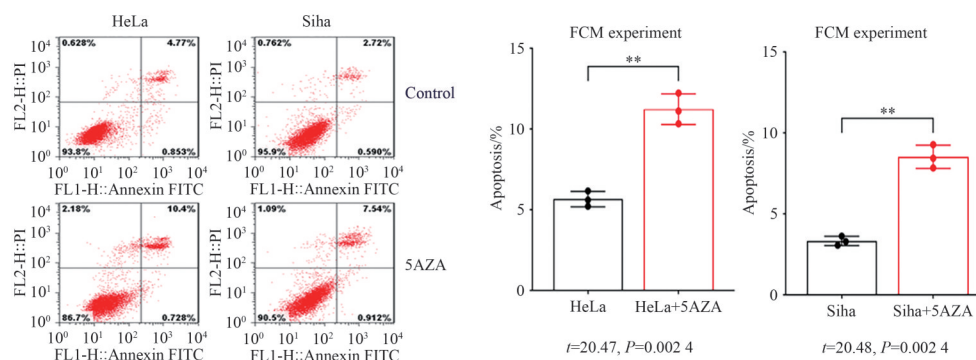


图 5 去甲基化对宫颈癌细胞凋亡的影响

Fig. 5 Effect of demethylation on the apoptosis of cervical cancer cells

本研究从转录和蛋白水平上分析 EPB41L3 基因在宫颈癌细胞与正常宫颈上皮细胞中的表达,结果显示,EPB41L3 在 HeLa 细胞和 SiHa 细胞中的表达水平均显著低于正常宫颈上皮细胞。

本课题组前期研究发现,EPB41L3 基因过表达不仅可抑制宫颈癌 HeLa 细胞和 SiHa 细胞的增殖和克隆形成能力,还可以阻滞细胞周期,促进细胞凋亡<sup>[19]</sup>。然而,EPB41L3 在宫颈癌中的作用机制尚不完全清楚。DNA 甲基化是一种可重复的物理表观遗传变化,涉及多种细胞过程,在肿瘤进展中发挥重要作用<sup>[20]</sup>。DNA 甲基化通常导致基因沉默,而 DNA 去甲基化与激活基因表达有关。当多个甲基转移到一个不应被甲基化的胞嘧啶上时,就会发生 DNA 超甲基化,从而导致基因沉默<sup>[21-22]</sup>。有学者证实,EPB41L3 甲基化可以区分宫颈标本中的癌前病变和浸润性病变。高级别宫颈上皮内瘤变(CIN2/3)女性患者中,EPB41L3 高甲基化出现在肿瘤发生前阶段<sup>[23-26]</sup>。本研究结果显示,EPB41L3 甲基化水平在慢性宫颈炎、高级别宫颈上皮内瘤变、宫颈癌组织中呈上升趋势,与文献报道一致。因此,EPB41L3 基因甲基化定量检测可能在宫颈癌筛查中有一定的应用价值。

EPB41L3 启动子高甲基化是卵巢癌、宫颈癌、弥漫性神经胶质瘤和前列腺癌发生的原因之一<sup>[27]</sup>。EPB41L3 启动子高甲基化是一种常见机制,可在肿瘤发展过程中下调 EPB41L3 表达,其重新表达则会诱导广泛的细胞凋亡。EPB41L3 通过调节肌动蛋白应力纤维的适当排列和促进与转移行为相关的细胞运动,可能在抑制肿瘤转移方面发挥重要作用<sup>[28]</sup>。研究表明,与癌旁正常组织相比,口腔鳞状细胞癌组织中 FLT3 和 EPB41L3 的甲基化水平显著升高(超甲基化)<sup>[27]</sup>。EPB41L3 在 hrHPV 阳性宫颈

癌患者中异常甲基化,且甲基化水平和频率随潜在病变严重程度的增加而增加<sup>[29]</sup>。有研究发现,用 5AZA 处理宫颈癌细胞可以恢复 EPB41L3 基因转录<sup>[30]</sup>。本研究结果显示,去甲基化药物 5AZA 可降低宫颈癌 HeLa 细胞和 SiHa 细胞的增殖和迁移能力,并促进其凋亡,提示 EPB41L3 在宫颈癌中可能因甲基化而无法发挥抑癌基因作用,其表达水平与宫颈癌进展可能呈正相关,可能是宫颈癌治疗的靶点之一。

本研究初步证实了 EPB41L3 基因甲基化对宫颈癌细胞的作用,但其调控机制尚不清楚,下一阶段研究将继续探索 EPB41L3 基因甲基化的调控机制。

### 参考文献

- [1] VU M, YU J, AWOLUDE O A, et al. Cervical cancer worldwide [J]. *Curr Probl Cancer*, 2018, 42(5): 457-465. DOI: 10.1016/j.currproblecancer.2018.06.003.
- [2] FANG J C, ZHANG H, JIN S F. Epigenetics and cervical cancer: from pathogenesis to therapy [J]. *Tumour Biol*, 2014, 35(6): 5083-5093. DOI: 10.1007/s13277-014-1737-z.
- [3] ZHANG Y J, XU R B, LI G Q, et al. Loss of expression of the differentially expressed in adenocarcinoma of the lung (DAL-1) protein is associated with metastasis of non-small cell lung carcinoma cells [J]. *Tumour Biol*, 2012, 33(6): 1915-1925. DOI: 10.1007/s13277-012-0452-x.
- [4] KITTINIYOM K, MASTRONARDI M, ROEMER M, et al. Allele-specific loss of heterozygosity at the DAL-1/4.1B (EPB41L3) tumor-suppressor gene locus in the absence of mutation [J]. *Genes Chromosomes Cancer*, 2004, 40(3): 190-203. DOI: 10.1002/gcc.20034.
- [5] BERNKOPF D B, WILLIAMS E D. Potential role of EPB41L3 (protein 4.1B/Dal-1) as a target for treatment of advanced prostate cancer [J]. *Expert Opin Ther Targets*, 2008, 12(7): 845-853. DOI: 10.1517/14728222.12.7.845.
- [6] YAMADA D, KIKUCHI S, WILLIAMS Y N, et al. Promoter hypermethylation of the potential tumor suppressor DAL-1/4.1B gene in renal clear cell carcinoma [J]. *Int J Can-*

- cer, 2006, 118(4): 916–923. DOI: 10.1002/ijc.21450.
- [7] VENETIANER R, CLARKE M A, VAN DER MAREL J, et al. Identification of HPV genotypes causing cervical precancer using tissue-based genotyping [J]. *Int J Cancer*, 2020, 146(10): 2836–2844. DOI: 10.1002/ijc.32919.
- [8] KABEKKODU S P, CHAKRABARTY S, GHOSH S, et al. Epigenomics, pharmacoepigenomics, and personalized medicine in cervical cancer [J]. *Public Health Genomics*, 2017, 20(2): 100–115. DOI: 10.1159/000475804.
- [9] LIONTOS M, KYRIAZOGLU A, DIMITRIADIS I, et al. Systemic therapy in cervical cancer: 30 years in review [J]. *Crit Rev Oncol Hematol*, 2019, 137: 9–17. DOI: 10.1016/j.critrevonc.2019.02.009.
- [10] HU Z, MA D. The precision prevention and therapy of HPV-related cervical cancer: new concepts and clinical implications [J]. *Cancer Med*, 2018, 7(10): 5217–5236. DOI: 10.1002/cam4.1501.
- [11] HELLER G, GERADTS J, ZIEGLER B, et al. Downregulation of TSLC1 and DAL-1 expression occurs frequently in breast cancer [J]. *Breast Cancer Res Treat*, 2007, 103(3): 283–291. DOI: 10.1007/s10549-006-9377-7.
- [12] QIU X L, GUAN X Y, LIU W X, et al. DAL-1 attenuates epithelial to mesenchymal transition and metastasis by suppressing HSPA5 expression in non-small cell lung cancer [J]. *Oncol Rep*, 2017, 38(5): 3103–3113. DOI: 10.3892/or.2017.6000.
- [13] YUAN X F, PIAO L H, WANG L H, et al. Pivotal roles of protein 4.1B/DAL-1, a FERM-domain containing protein, in tumor progression (Review) [J]. *Int J Oncol*, 2019, 55(5): 979–987. DOI: 10.3892/ijo.2019.4877.
- [14] DAFOU D, GRUN B, SINCLAIR J, et al. Microcell-mediated chromosome transfer identifies EPB41L3 as a functional suppressor of epithelial ovarian cancers [J]. *Neoplasia*, 2010, 12(7): 579–589. DOI: 10.1593/neo.10340.
- [15] GUTMANN D H, DONAHOE J, PERRY A, et al. Loss of DAL-1, a protein 4.1-related tumor suppressor, is an important early event in the pathogenesis of meningiomas [J]. *Hum Mol Genet*, 2000, 9(10): 1495–1500. DOI: 10.1093/hmg/9.10.1495.
- [16] GUO H N, ZHANG R, AFRIFA J, et al. Decreased expression levels of DAL-1 and TOB1 are associated with clinicopathological features and poor prognosis in gastric cancer [J]. *Pathol Res Pract*, 2019, 215(6): 152403. DOI: 10.1016/j.prp.2019.03.031.
- [17] CHARBONEAU A L, SINGH V, YU T X, et al. Suppression of growth and increased cellular attachment after expression of DAL-1 in MCF-7 breast cancer cells [J]. *Int J Cancer*, 2002, 100(2): 181–188. DOI: 10.1002/ijc.10470.
- [18] KIKUCHI S, YAMADA D, FUKAMI T, et al. Promoter methylation of DAL-1/4.1B predicts poor prognosis in non-small cell lung cancer [J]. *Clin Cancer Res*, 2005, 11(8): 2954–2961. DOI: 10.1158/1078-0432.ccr-04-2206.
- [19] TUERXUN G, ABULIMITI T, ABUDUREXITI G, et al. Overexpression of EPB41L3 promotes apoptosis of human cervical carcinoma cells through PI3K/AKT signaling [J]. *Acta Biochim Pol*, 2022, 69(2): 283–289. DOI: 10.18388/abp.2020\_5649.
- [20] MAHMOUD A M, ALI M M. Methyl donor micronutrients that modify DNA methylation and cancer outcome [J]. *Nutrients*, 2019, 11(3): 608. DOI: 10.3390/nu11030608.
- [21] EHRLICH M, LACEY M. DNA methylation and differentiation: silencing, upregulation and modulation of gene expression [J]. *Epigenomics*, 2013, 5(5): 553–568. DOI: 10.2217/epi.13.43.
- [22] FUKUSHIGE S, HORII A. DNA methylation in cancer: a gene silencing mechanism and the clinical potential of its biomarkers [J]. *Tohoku J Exp Med*, 2013, 229(3): 173–185. DOI: 10.1620/tjem.229.173.
- [23] VERLAAT W, VAN LEEUWEN R W, NOVIANTI P W, et al. Host-cell DNA methylation patterns during high-risk HPV-induced carcinogenesis reveal a heterogeneous nature of cervical pre-cancer [J]. *Epigenetics*, 2018, 13(7): 769–778. DOI: 10.1080/15592294.2018.1507197.
- [24] VASILJEVIĆ N, SCIBIOR-BENTKOWSKA D, BRETNALL A R, et al. Credentialing of DNA methylation assays for human genes as diagnostic biomarkers of cervical intraepithelial neoplasia in high-risk HPV positive women [J]. *Gynecol Oncol*, 2014, 132(3): 709–714. DOI: 10.1016/j.ygyno.2014.02.001.
- [25] BRETNALL A R, VASILJEVIĆ N, SCIBIOR-BENTKOWSKA D, et al. A DNA methylation classifier of cervical precancer based on human papillomavirus and human genes [J]. *Int J Cancer*, 2014, 135(6): 1425–1432. DOI: 10.1002/ijc.28790.
- [26] BOERS A, WANG R, VAN LEEUWEN R W, et al. Discovery of new methylation markers to improve screening for cervical intraepithelial neoplasia grade 2/3 [J]. *Clin Epigenetics*, 2016, 8: 29. DOI: 10.1186/s13148-016-0196-3.
- [27] KHONGSTI S, SHUNYU B N, GHOSH S. Promoter-associated DNA methylation & expression profiling of genes (*FLT3*, *EPB41L3* & *SFN*) in patients with oral squamous cell carcinoma in the *Khasi & Jaintia* population of Meghalaya, India [J]. *Indian J Med Res*, 2019, 150(6): 584–591. DOI: 10.4103/ijmr.IJMR\_620\_18.
- [28] ZENG R, HUANG J P, LI X F, et al. Epb41l3 suppresses esophageal squamous cell carcinoma invasion and inhibits MMP2 and MMP9 expression [J]. *Cell Biochem Funct*, 2016, 34(3): 133–141. DOI: 10.1002/cbf.3170.
- [29] LI N, HU Y J, ZHANG X Y, et al. DNA methylation markers as triage test for the early identification of cervical lesions in a Chinese population [J]. *Int J Cancer*, 2021, 148(7): 1768–1777. DOI: 10.1002/ijc.33430.
- [30] GUERRERO-SETAS D, PÉREZ-JANICES N, BLANCO-FERNANDEZ L, et al. RASSF2 hypermethylation is present and related to shorter survival in squamous cervical cancer [J]. *Mod Pathol*, 2013, 26(8): 1111–1122. DOI: 10.1038/modpathol.2013.32.

校稿: 李征 于静

本文引用格式: 张媛媛, 朱江, 赵静, 等. EPB41L3 基因甲基化参与调控宫颈癌进展的相关性研究[J]. 肿瘤药 学, 2024, 14(5): 554–559. DOI: 10.3969/j.issn.2095-1264.2024.05.06.

Cite this article as: ZHANG Yuanyuan, ZHU Jiang, ZHAO Jing, et al. Correlation between methylation of EPB41L3 gene and regulation of cervical cancer progression [J]. *Anti-tumor Pharmacy*, 2024, 14(5): 554–559. DOI: 10.3969/j.issn.2095-1264.2024.05.06.