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食管鳞癌血管生成拟态的组织学和细胞学研究 *

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摘要 目的：探讨血管生成拟态(vasculogenic mimicry，VM)与食管鳞癌临床病理特征的关系及其对患者预后的影响，并分析食管癌血管生成拟态的形成机制。**方法：**收集 57 例食管鳞癌石蜡包埋样本，进行过碘酸雪夫氏(PAS)及 CD34 免疫组织化学双重染色，结合 HE 染色，观察食管鳞癌血管生成拟态的发生情况。对患者临床病理和预后信息进行单因素分析，Kaplan-Meier 生存比较和 Cox 风险模型分析。通过食管鳞癌细胞株 Eca-109 三维培养建立，观察 RNAi 沉默 VE-cadherin 对食管鳞癌 Eca109 血管生成拟态形成的影响。**结果：**食管鳞癌中 VM 表达的阳性率为 54.3%，显著高于正常食管黏膜组织；VM 在病理分型为低分化食管鳞癌的阳性表达率为 78.9%，显著高于中高分化组(P<0.05)；III-Ⅳ期食管鳞癌患者 VM 阳性率显著高于Ⅰ-Ⅱ期食管鳞癌患者(P<0.05)；有淋巴结转移的食管鳞癌者 VM 阳性率明显高于无淋巴结转移者(P<0.05)。单因素分析结果显示食管鳞癌 VM 的发生率与肿瘤的分化程度、TNM 分期和淋巴转移显著相关。Kaplan-Meier 生存分析显示有 VM 组食管鳞癌患者的生存期明显短于无 VM 组(P<0.05)；Cox 分析显示 VM 是影响食管鳞癌患者预后的独立危险因素(RF=0.67)。三维培养结果显示 Eca-109 细胞在基质胶上形成典型的血管网状样结构，VE-cadherin-siRNA 可有效抑制 VE-cadherin 在 Eca109 的表达，抑制体外培养的 Eca109 细胞 VM 的形成。**结论：**血管生成拟态是食管鳞癌一种独特的血液供应模式，与食管鳞癌的分化程度、TNM 分期、淋巴转移密切相关，是食管鳞癌患者术后生存期的独立危险因素。

关键词：食管鳞癌；血管生成拟态；预后

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Histology and Cytology Research on the Vasculogenic Mimicry in the Esophageal Squamous Cell Carcinomas*

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ABSTRACT Objective: To investigate the relationship between vasculogenic mimicry (Vasculogenic mimicry, VM) and clinicopathological features of esophageal squamous cell carcinoma and its influence on the prognosis of the patients, and analyze the mechanism of VM formation in the esophageal cancer. **Methods:** A total of 57 cases of ESCC paraffin bag buried samples and periodic acid Schiff (PAS) and CD34 immunohistochemical double staining, combined with HE staining were selected, the occurrence of vasculogenic mimicry in esophageal squamous cell carcinoma was observed. Combined with the clinical pathology and prognosis information, the correlation parameters were analyzed by univariate analysis, Kaplan-Meier survival comparison and Cox risk model analysis. Through the three-dimensional culture of esophageal squamous cell carcinoma cell line Eca-109 were established in the effect of RNAi silencing of VE cadherin in esophageal squamous cell carcinoma Eca109 vasculogenic mimicry formation. **Results:** The positive rate of VM expression in the esophageal squamous cell carcinoma was 54.3%, which was significantly higher than that in the normal esophageal mucosa; The positive expression rate of VM expression in the poorly differentiated squamous cell carcinoma was 78.9%, which was significantly higher than that in highly differentiated group (P<0.05). The positive expression rate of VM expression in the Stage III-IV esophageal squamous cell carcinoma was significantly higher than that of esophageal squamous cell carcinoma patients with stage I and II (P<0.05). The positive expression rate of VM expression in the esophageal squamous cell carcinoma with lymph node metastasis was significantly higher than those without lymph node metastasis (P<0.05). Univariate analysis showed that the incidence of VM in esophageal squamous cell carcinoma was closely related to the degree of tumor differentiation, TNM stage and lymph node metastasis. Kaplan-Meier survival analysis showed that there was significantly shorter survival than no VM group, Cox analysis showed that VM was an independent risk factor for the prognosis of patients with esophageal squamous cell carcinoma (RF=0.67, VM). Three dimensional culture results showed that Eca-109 cells in Matrigel formed typical vascular network like structure. VE-cadherin-siRNA can effectively inhibit VE-cadherin ex-

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pression in Eca109, inhibit the formation of in vitro cultured Eca109 cell VM. **Conclusion:** Vasculogenic mimicry isunique pattern of blood supply that is closely related to the differentiation, TNM stage, lymph node metastasis of esophageal squamous cell carcinoma, and it is an independent risk factor for survival in the postoperative patients with esophageal squamous cell carcinoma.

Key words: Esophageal squamous cell carcinoma; Vasculogenic mimicry; Prognosis

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前言

食管癌是消化道系统常见的恶性肿瘤,鳞癌是其主要组织学类型,食管癌发病率和死亡率在全部恶肿瘤均居前列,总体治疗效果差[1,2]。血管生成拟态(vasculogenic mimicry,VM)是近年通过研究发现的一种独立于机体内皮细胞的肿瘤微循环模式,其生长方式与经典的肿瘤血管生长方式截然不同。VM 的形成可为迅速增殖肿瘤提供血运,缓解肿瘤周围缺血缺氧微环境,进一步加速肿瘤的侵袭及转移,其形成与肿瘤患者临床分期及远期预后密切相关[3,4]。

血管内皮钙粘着素 (vascular endothelial cadherin,VE-cadherin/VE-cad)是一种特异的跨膜粘附蛋白,其附着于血管内皮细胞表面,可保持血管的完整性,促进相邻内皮细胞之间的粘附[5,6]。近年的研究显示高表达 VE-cad 可能是肿瘤血管生成拟态的重要调节机制[7,8]。本研究主要分析了食管鳞癌组织内 VM 表达及其与患者临床预后的相关性，并进一步探讨了 VE-cad 对 VM 形成的影响，以期为以 VM 作为靶点进行食管癌的临床诊断和治疗提供新的思路。

1 材料与方法

1.1 临床资料

选择 2014 年 12 月至 2017 年 1 月于哈尔滨医科大学附属第一医院胸外科接受手术治疗且病例资料保存完好的食管鳞状细胞癌组织蜡块标本共计 57 例，所有患者的临床资料均完整、无失访,其中男性患者共 51 例,女性患者共 6 例;年龄 41 岁至 72 岁,中位年龄 58 岁;高分化癌 10 例,中分化癌 28 例,低分化癌 19 例;TNM 分期 (依据 AJCC,2009 第 7 版),I-Ⅱ期 15 例,Ⅲ-Ⅳ期 42 例;无淋巴结转移者 17 例,有淋巴结转移者 40 例;且上述所有患者术前均未接受任综合治疗。

1.2 细胞、主要试剂

人食管鳞癌细胞株 Eca-109 哈尔滨医科大学中心实验室传代保存。IMDM 培养基、胰蛋白酶(美国 Gibco 公司)、小牛血清(杭州四季青生物材料公司)、四甲基偶氮唑蓝(MTT)(美国 sigma 公司);Elivison TM plus 试剂盒，鼠抗人 CD34 单克隆抗体购自福州迈新生物技术开发公司;PAS 染液为哈尔滨医科大学第一附属医院病理科配制。

1.3 VM 观察

石蜡标本连续切片后烤干(厚度:4 μm/ 张),于二甲苯、梯度乙醇中脱蜡至水,苏木素浅染细胞核、盐酸酒精分化、返蓝、伊红染色,乙醇脱水、二甲苯透明、中性树胶封片,完成 HE 染色。采用 Elivison TM plus 法进行免疫组织化学染色,CD34 染色,DAB 显色后,应用水流冲洗 1 分钟终止显色反应,将切片置于浓度为 0.5%的高碘酸溶液中氧化 10 分钟。再以流水冲洗 2 分钟后置于 Schiff 中染色 15 至 30 分钟，蒸馏水连续冲洗 3 次,每次冲洗 1 分钟,此后依次苏木素浅染细胞核、盐酸酒精分化、返蓝、脱水透明以及中性树胶封片。VM 判断方法为管壁由肿瘤细胞围绕 PAS 阳性而 CD34 阴性的管道，管腔内可有或无红细胞,附近少见坏死肿瘤细胞及炎细胞浸润。管壁有 CD34 阳性的内皮细胞为内皮依赖性血管。

1.4 体外三维培养系统 VM 形成的观察

将 96 孔板置于冰上,在冰上将 1×10^3 个处于对数生长期的人食管鳞癌细胞株与 Eca-109Matrigel 胶等体积混合制成细胞悬液,接种于 96 孔板,迅速放入 37 ℃孵箱孵育 2 分钟,胶化后向每孔加入并覆盖 100 μL 的完全培养液，置于孵化箱中培养(37℃ 、饱和度:5% CO_2)。每 24 h 更换培养液。分别在 24 h、48 h、72 h、96 h 于倒置显微镜下(× 400),随机选取视野观察并记录细胞的生长状态及 VM 形成情况。

1.5 VE-cadherin-siRNA 的构建及转染

构建含有 VE-cadherin 的 siRNA 序列表达载体 pslincer3.1/VE-cadherin。将 Eca-109 细胞接种于 6 孔板，待其生长至 80%汇合时，重组质粒 pslincer3.1/VE-cadherin、pslincer3.1/NC(阴性对照)、未转染组细胞以脂质体 Lipofectamine2000 辅助转染 Eca-109 细胞(质粒:脂质体 =1:3),各设 3 复孔。siRNA 干扰序列为,正义链:5-GGAACCAGAUGCACAUUGAUU-3;反义链:5-UCAAUGUGCAUCUGGUUCCUU-3,序列由上海吉玛公司合成。

1.6 统计学分析

运用 SPSS19.0 统计软件进行数据分析处理，采用卡方检验分析 VM 的表达与食管鳞状细胞癌患者的年龄、性别、部位、瘤体大小、有无淋巴结转移、肿瘤分化程度及 TNM 分期等因素的关系;采用 Kaplan-meier 生存曲线分析,生存时间的比较采用 log-rank 检验,以 $P<0.05$ 为差异有统计学意义。

2 结果

2.1 食管鳞癌 VM 的表达

通过 CD34 与 PAS 双重染色，结合 HE 染色切片筛选,57 例食管鳞癌组织中,有 31 例存在 VM 结构管道(54.38%);而正常食管粘膜组织中不存在 VM 现象，其 VM 的发生率比较差异具有统计学意义($P<0.05$)。食管鳞癌组织中 VM 的存在与患者的年龄、性别、食道部位、肿瘤大小无关。

2.2 食管鳞癌中 VM 的表达与临床病理参数的关系

通过进一步对食管鳞癌组织中 VM 的存在与淋巴转移、不同 TNM 分期及病理分型的分析,结果显示有淋巴结转移的食管鳞癌患者 VM 阳性率为[70.0%(28/40)],明显高于无淋巴结转移组 [17.6%(3/17)]; 低分化组食管鳞癌患者 VM 阳性率[78.9%(15/19)],显著高于中高分化组[44.7%(17/38)];I-Ⅱ期食管鳞癌患者组 VM 阳性率为 [20.0%(3/15)]，低于 III 期 -Ⅳ期[66.6%(28/42)]($P<0.05$)。

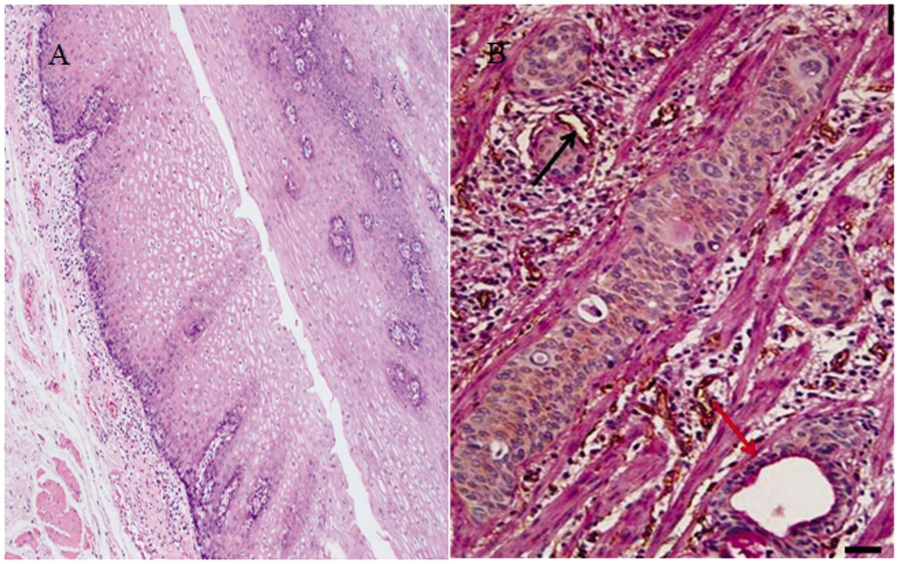

图 1 正常食管及食管鳞癌 VM 染色 A:正常食管无 VM 结构;B:红色箭头所示为 CD34 阴性的肿瘤细胞,黑色箭头所示为 CD34 染色阳性的上皮。(× 400)

Fig.1 Staining of normal esophagus and esophageal squamous cell carcinoma VM A: There is no VM in normal esophagus. B: The red arrow shows CD34 negative tumor cells and the black arrow shows CD34 positive epithelium(× 400)

表 1 食管鳞癌中 VM 的表达与临床病理参数的关系

Table 1 Relationship between VM expression and clinicopathological parameters in the esophageal squamous carcinoma

Groups	n	VM		x^2 Value	*P* Value
		+	-		
Normal esophageal tissue	21	0	21	19.45	*P*<0.05
Squamous carcinoma tissue	57	31	26		
TNM					
I-Ⅱ	15	3	12	9.703	*P*<0.05
Ⅲ-Ⅳ	42	28	14		
Degree of differentiation					
Medium to high differentiation	38	17	21	6.021	*P*<0.05
Poorly differentiated	19	15	4		
Lymphatic metastasis					
Yes	40	28	12	13.18	*P*<0.05
No	17	3	14		

2.3 生存分析

Kaplan-Meier 生存曲线结果显示 VM 阳性组生存期明显低于 VM 阴性组 (Log-rank 检验,x^2=4.189,*P*=0.041<0.05),VM 阳性组 36 个月生存率约为 16.1%,低于 VM 阴性组(45.8%)。

2.4 VE-cadherin siRNA 对 Eca109 细胞体外三维培养的影响

qRT-PCR 和 western blot 检测结果显示转染 VE-cadherin siRNA 后，与对照组相比,Eca109 细胞 VE-cadherin 表达均明显下调。VE-cadherin 的表达降低导致 Eca109 细胞管腔形成数量显著降低。

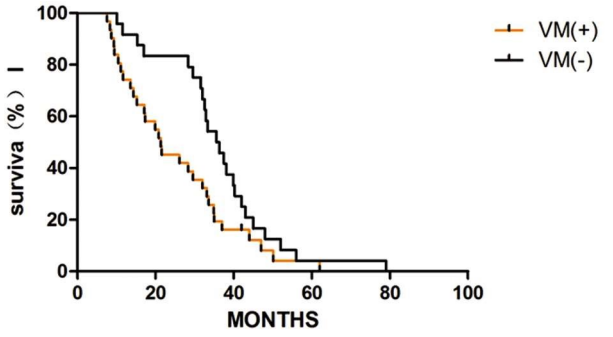

图 2 VM 表达对食管癌患者术后的生存曲线的影响

Fig.2 Effect of VM expression on the survival of patients with esophageal cancer after surgery

3 讨论

血液供应是保证实体瘤持续生长和发生血行转移的重要

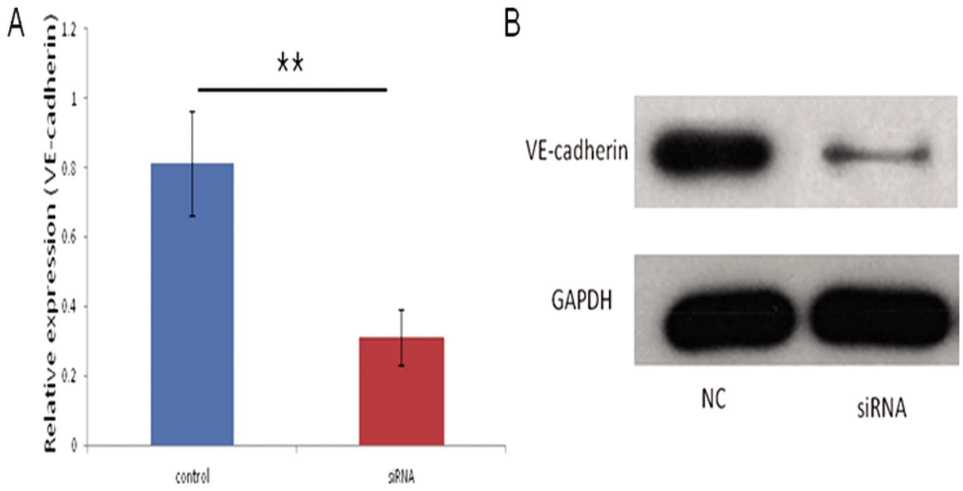

图 3 VE-cadherin siRNA 转染后 VE-cadherin mRNA 和蛋白质表达

A:qRT-PCR 检测 VE-cadherin mRNA 表达;B:Westernblot 检测VE-cadherin 蛋白质表达。

Fig.3 VE-cadherin mRNA and protein expression after VE-cadherin siRNA transfection

A: VE-cadherin mRNA tested by qRT-PCR; B: VE-cadherin protein expression tested by Westernblot.

物质基础,靶向抑制肿瘤血管生成已经成为肿瘤治疗研究的热点[9-11]。VM 被证实生长途径不同于经典肿瘤血管生结构、不依赖内皮且与肿瘤侵袭、转移及患者预后密切相关[3,14]。研究表明乳腺癌、卵巢癌、前列腺癌、骨肉瘤等恶性肿瘤中 VM 的存在促进肿瘤细胞有更强的侵袭和转移能力,导致其临床预后较差的重要因素[3-4,12-19]。

我国食管癌发病率为 13/10 万,大多数患者就诊时已属于临床中晚期,肿瘤的进展快,预后差[1,20-22]。VM 的存在情况可能也是导致食管癌预后差的一项主要因素。我们通过对 57 例食管鳞癌的回顾性分析证实在 31 例食管癌组织标本中发现了 VM 的存在。通过对食管鳞癌 VM 的表达特点及其与病人临床各参数的统计分析发现,食管鳞癌组织中 VM 的存在与患者的年龄、性别、病变生长部位、瘤体大小无关。VM 的阳性表达与反应肿瘤恶性程度的肿瘤分化水平、肿瘤生物学特性的 TNM 分期及肿瘤侵袭转移能力的淋巴结转移均密切相关,这一结论与国内外探索 VM 与食管癌的相关研究结论相一致[5],充分说明 VM 是导致食管癌患者预后不良的重要影响因素。我们通过 Kaplan-Meier 生存分析结果得知,VM 阳性表达是一项有效的食管癌患者生存期判断指标。

VM 的发生机制目前尚不分清楚,实体瘤缺氧微环境,HIF-1 分子和 VEGF 分子的异常表达,细胞内磷酸肌醇三激酶 PI3K 信号通路的活化等均被认为是促进 VM 形成的调节因素[3,23,24]。VE-cadherin 是一种粘附蛋白,介导细胞之间互相粘附,维持肿瘤血管的进一步生成,加速肿瘤细胞的侵袭能力和转移能力。VE-cadherin 可以通过和 EphA2、FAK、PI3K、MMP2 等分子之间的相互影响促进了 VM 的形成[4,25]。我们通过体外的三维培养研究发现,具有 VM 形成能力的 Eca-109 细胞由于 VE-cadherin 表达水平的降低,而 VM 形成能力显著下降,说明 VE-cadherin 在食管癌 VM 形成占有重要的作用。结合 Heinolainen K 及 Han H 等[26-28]研究,我们推测 VE-cadherin 可能是食管癌发生 VM 的重要决定因素。

VM 的提出为解释恶性肿瘤的血液转移机制及恶性肿瘤的血液供应机制提供了新的理论基础,也为恶性肿瘤的抗血管生成等新型治疗方案提供了理论依据。在多种恶性肿瘤中 VM 形成的实验研究中均已证实,VM 与肿瘤的生长、侵袭、转移及预后等多项指标密切相关[3,4,12-18]。部分恶性肿瘤通过抗内皮细胞治疗其疗效欠佳,其原因也可通过 VM 现象来解释[29,30],归纳其原因可能与肿瘤的血液供应包括血管生成途径外,还可以通过血管生成拟态来获得有关。

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