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【论著与临床报道】

TIAM2在食管鳞癌中的表达及临床意义

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摘要:目的 探讨 TIAM2 在食管鳞癌中的表达及意义。方法 采用免疫组化 SP 法检测 108 例食管鳞癌、42 例正常食管组织中 TIAM2 蛋白的表达情况。结果 TIAM2 在食管鳞癌中表达的阳性率为 78.70%,明显高于正常食管组织 19.05% ($P < 0.05$)。食管鳞癌的组织学分级级别越高, TIAM2 表达阳性率越高; TNM 分期中 III ~ IV 期的 TIAM2 表达阳性率高于 I ~ II 期; 有浆膜层浸润的 TIAM2 表达阳性率高于无浆膜层浸润; 有淋巴结转移的 TIAM2 表达阳性率高于无淋巴结转移 ($P < 0.05$), 但与食管鳞癌患者的年龄及性别无关 ($P > 0.05$)。结论 TIAM2 在食管鳞癌中表达上调, TIAM2 可能参与食管鳞癌的发生发展及转移过程。

关键词:食管肿瘤; TIAM2; 免疫组化

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Expression and clinical significance of TIAM2 in esophageal squamous cell carcinoma

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Abstract: **Objective** To investigate the expression and significance of TIAM2 in esophageal squamous cell carcinoma. **Methods** This study detected the expression of TIAM2 protein by SP immunohistochemical method in 108 cases of esophageal squamous cell carcinoma and 42 cases of normal esophageal tissues. **Results**

The positive rate of TIAM2 expression in esophageal squamous cell carcinoma was 78.70%, which was significantly higher than that in normal esophageal tissues (19.05%, $P < 0.05$). The higher the histological grade of esophageal squamous cell carcinoma, the higher was the positive expression rate of TIAM2. In TNM stages, the positive rate of TIAM2 expression in stage III ~ IV was higher than that in stage I ~ II. The positive rate of TIAM2 expression in cases with serous layer infiltration was higher than that without serous layer infiltration. The positive rate of TIAM2 expression in cases with lymph node metastasis was higher than that without lymph node metastasis ($P < 0.05$), but it was not related to age and gender of patients with esophageal squamous cell carcinoma ($P > 0.05$). **Conclusion** TIAM2 expression is up-regulated in esophageal squamous cell carcinoma, and TIAM2 may be involved in the occurrence, development and metastasis of esophageal squamous cell carcinoma.

Key words: esophageal squamous cell carcinoma; TIAM2; immunohistochemistry

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食管癌是源于食管黏膜上皮或腺体的恶性肿瘤,其组织学类型分为鳞癌、腺癌、腺鳞癌、小细胞癌等多种类型,中国以鳞癌最多见,占90%以上^[1-2]。食管癌具有发病率高、转移性强、早期诊断率低、死亡率高等特点^[3]。肿瘤的浸润和转移是影响患者预后的主要原因,所以探讨肿瘤浸润及转移相关机制是当今医学研究的热点。T淋巴瘤侵袭转移诱导因子2(T-cell lymphoma invasion and metastasis factor2, TIAM2)基因是TIAM1的同源物, TIAM1在正常脑组织和恶性肿瘤中的作用已明确,但是TIAM2的功能还不清楚。TIAM2在食管癌中的表达的研究国内外少见报道,本研究通过免疫组化SP法检测TIAM2在食管鳞癌中的表达,探讨TIAM2在食管鳞癌发生发展中的作用,报告如下。

1 资料和方法

1.1 病例资料 研究组:食管鳞癌108例,对照组:正常食管组织42例,来自手术标本切缘,离癌肿5cm以上。研究组标准:经病理诊断为食管鳞癌,患者术前未经治疗,且无其他恶性肿瘤病史。研究组中男性73例,女性35例;年龄41~81岁,平均年龄为(62.00±5.26)岁。

1.2 试剂 兔抗人TIAM2抗体购自美国Abcam公司,免疫组化SP法试剂盒和DAB显色试剂盒购自福州迈新公司。

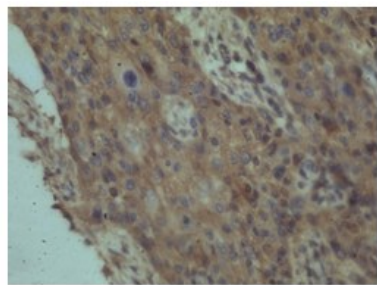


图1 TIAM2在食管鳞癌中的阳性表达(免疫组化,SP法,×400)

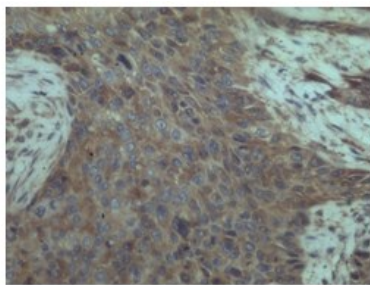


图2 阳性对照图片(免疫组化,SP法,×400)

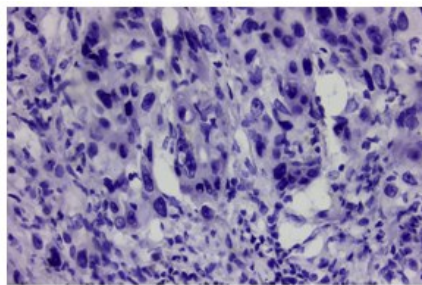


图3 阴性对照图片(免疫组化,SP法,×400)

2.1 TIAM2在食管鳞癌及正常食管组织中的表达 TIAM2在食管鳞癌中表达的阳性率明显高于正常食管组织,差异有统计学意义($P < 0.001$),见表1。

表1 TIAM2在食管鳞癌及癌旁正常食管组织中的表达

组别	n	TIAM2		阳性率/%	χ^2	P
		-	+			
食管鳞癌组织	108	23	85	78.70	44.512	<0.001
正常食管组织	42	34	8	19.05		

2.2 TIAM2蛋白表达与食管鳞癌临床病理特征的关系 TIAM2蛋白表达阳性率与食管鳞癌的病理分级、

1.3 标本检测 TIAM2免疫组化染色采用SP法,主要步骤:石蜡标本切片厚度4 μ m,脱蜡至水、3% H_2O_2 孵育灭活内源性过氧化物酶活性,置于枸橼酸钠缓冲溶液进行高压抗原修复,血清封闭,滴加TIAM2抗体于4℃冰箱孵育过夜,滴加二抗室温孵育1h, DAB显色,苏木素复染,脱水,透明,封片。用已知阳性切片作为阳性对照,用PBS缓冲液替代一抗作为阴性对照。

1.4 结果判定 TIAM2阳性判断标准:①着色部位判断标准:TIAM2染色位于细胞质,呈浅黄色、棕黄色或棕褐色为阳性;②着色强度:无着色记0分、浅黄记1分、棕黄记2分、棕褐色记3分;③阳性细胞比例:在400倍显微镜下计数200个肿瘤细胞,<10%记0分,10%~25%记1分,25%~50%记2分,>50%记3分。两项评分结果相乘作为最终得分:0~3分记为低表达记阴性(-), ≥ 4 分记为高表达记阳性(+)

1.5 统计学方法 采用SPSS 18.0统计软件对数据进行统计分析,计数资料采用 χ^2 检验,以 $P < 0.05$ 为差异具有统计学意义。

2 结果

TIAM2阳性染色主要在细胞质,呈浅黄色、棕黄色或棕褐色,见图1。阳性对照图片见图2,阴性对照图片见图3。

TNM分期、浸润深度及淋巴结转移有关($P < 0.05$),而与患者的性别和年龄无关,见表2。

3 讨论

人类基因TIAM2位于染色体6q25.2上,其转录产生两个mRNA亚型,短转录本编码有626个残基的蛋白质TIAM2S,长转录本编码有1701个氨基酸残基的蛋白质TIAM2L^[4],这些蛋白是鸟苷酸交换因子TIAM的亚家族成员。TIAM1是人类TIAM2的同源物, TIAM1在人类恶性肿瘤和神经元发育中起重要作用,可特异性激活Rac-1,通过TIAM1-Rac信号途径改变肿瘤细胞的形态,诱导肿瘤的侵袭转移,作为一种癌蛋白, TIAM1过表达有助于多种不同类型的恶性

表 2 TIAM2 蛋白表达与食管鳞癌临床病理特征的关系

临床病理特征	n	TIAM2			χ^2	P
		-	+	阳性率/%		
性别					0.603	0.437
男	73	14	59	80.82		
女	35	9	26	74.28		
年龄/岁					1.459	0.227
≥60	68	12	56	82.35		
<60	40	11	29	72.50		
病理分级					9.796	0.007
I	37	14	23	62.16		
II	45	7	38	84.44		
III	26	2	24	92.31		
TNM 分期					4.837	0.028
I~II	68	19	49	72.06		
III~IV	40	4	36	90.00		
浸润浆膜层					9.358	0.002
有	63	7	56	88.89		
无	45	16	29	64.44		
淋巴结转移					8.164	0.004
有	52	5	47	90.38		
无	56	18	38	67.86		

肿瘤的发生,并与肿瘤细胞的侵袭、转移、恶性程度及预后关系密切^[5-6],包括肠癌^[7]、胰腺癌^[8]、宫颈癌^[9]、肺癌等^[10]。而 TIAM1 和 TIAM2 在正常脑组织中富集,是神经元生长、发育所必需的,参与调节大脑神经的运动性和可塑性^[4,11-12]。

TIAM2 在肿瘤中的研究较少,主要在肺癌和肝癌中有研究。Zhao ZY 等^[13]研究发现 TIAM2 在非小细胞肺癌中高表达;沉默 TIAM2 在肺癌细胞的表达,可抑制细胞侵袭和运动能力,也抑制 Rac1 的激活;下调 TIAM2 可上调 E-cadherin 的表达,下调 MMP-3、Twist 和 Snail 的表达;Rac1 的激活和一些侵袭相关基因的调控可能参与了这一过程。Li SK 等^[14]研究发现 TIAM2 在原发性肺癌相关成纤维细胞中的表达水平明显高于正常肺成纤维细胞,TIAM2 沉默成纤维细胞的迁移和侵袭能力下降;在直接共培养体系中,与 TIAM2 沉默成纤维细胞共培养时,癌细胞的迁移和侵袭受到阻滞,认为成纤维细胞 TIAM2 促进肺癌细胞的侵袭和转移。Chen JS 等^[15]研究发现 TIAM2S 在肝癌中高表达,而在正常肝细胞中不表达,同时 TIAM2S 表达与 TIAM1 呈正相关,TIAM2S 表达增加促进肝癌细胞的上皮-间充质转化,导致肝癌细胞的增殖和侵袭。

本研究发现 TIAM2 在食管鳞癌中呈高表达,且与食管鳞癌的病理分级、TNM 分期、浸润深度及淋巴结转移有关,因此笔者推测,TIAM2 作为增殖调控基因,可能参与了人类肿瘤的发生,同时有促进肿瘤的侵袭和转移作用。已有学者研究认为 TIAM2 可能通过

以下机制发挥其促癌作用:TIAM2 可能直接与激活的 Rho 家族 GTPases 结合,触发下游信号;或者,TIAM2 可以直接与下游的支架蛋白结合,激活信号传导并发挥其致瘤效应^[15]。随着研究的深入,TIAM2 对肿瘤发生发展的相关机制将逐步被阐明。

总之,TIAM2 蛋白可能在食管癌的发生、发展中发挥了重要的作用,其有望成为食管癌重要标志物和分子治疗靶点。

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