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大肠癌组织 Ets-1, MMP-1 和 VEGF 的表达及意义

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Expression of E26 transformation-specific-1, matrix metalloproteinases-1 and vascular endothelial growth factor in colorectal carcinoma

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Abstract

AIM: To study the expression of E26 transformation-specific-1 (Ets-1), matrix metalloproteinases-1 (MMP-1) and vascular endothelial growth factor (VEGF) in human colorectal carcinoma, and to explore the role of Ets-1 in the angiogenesis and metastasis of carcinoma.

METHODS: The expression of Ets-1, MMP-1 and VEGF were detected in colorectal carcinoma (n = 61) and normal colon tissues (n = 21) by the immunohistochemical method respectively.

RESULTS: Ets-1, MMP-1 and VEGF were negatively expressed in all normal mucosal tissues. The positive rates of Ets-1, MMP-1 and VEGF expression were 75.4%, 78.7% and 82.0% in colorectal carcinoma respectively. No significant correlation was found between their positive rates and tumor's size as well as the differentiation (P >0.05). The expression of Ets-1, MMP-1 and VEGF were significantly correlated with Duke's staging (χ^2 = 10.718, P <0.01; χ^2 = 8.323, P <0.01; χ^2 = 6.145, P <0.05), the depth of invasion (χ^2 = 7.705, P <0.01; χ^2 = 19.101, P <0.01; χ^2 = 14.707, P <0.01), lymphatic invasion (χ^2 = 9.333, P <0.01; χ^2 = 3.965, P <0.05; χ^2 = 4.638, P <0.05) and distant metastasis (χ^2 = 5.472, P <0.05; χ^2 = 4.125, P <0.05; χ^2 = 5.034, P <0.05). Ets-1 expression was positively associated with MMP-1 and VEGF level (r = 0.447, P <0.01; r = 0.425, P <0.05).

CONCLUSION: Ets-1 was over-expressed in colorectal carcinoma, and its expression was related to clinical staging, invasion and metastasis. Ets-1 expression was also positively related to MMP-1 and VEGF level. Their expression can become referential indexes to predict the malignant behavior of colorectal carcinoma.

Key Words: E26 transformation-specific-1, Matrix metalloproteinases-1; Vascular endothelial growth factor; Colorectal carcinoma

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摘要

目的: 检测大肠癌中转录因子Ets-1, 基质金属蛋白酶-1(MMP-1)和血管内皮生长因子(VEGF)的表达, 探讨Ets-1在大肠癌血管生成和浸润转移中的作用.

方法: 应用免疫组化SP法检测61例大肠癌组织和21例正常大肠组织中Ets-1, MMP-1和VEGF蛋白的表达水平.

结果: Ets-1, MMP-1和VEGF在正常大肠黏膜中表达均为阴性. 在大肠癌组织中表达的阳性率分别为75.4%, 78.7%和82.0%. 其表达水平与肿瘤大小和分化程度无关(P>0.05), 与Duke's分期(χ^2 = 10.718, P<0.01; χ^2 = 8.323, P<0.01; χ^2 = 6.145, P<0.05)、浸润深度(χ^2 = 7.705, P<0.01; χ^2 = 19.101, P<0.01; χ^2 = 14.707, P<0.01)、淋巴结转移(χ^2 = 9.333, P <0.01; χ^2 = 3.965, P<0.05; χ^2 = 4.638, P<0.05)和远处转移(χ^2 = 5.472, P<0.05; χ^2 = 4.125, P<0.05; χ^2 = 5.034, P<0.05)密切相关. 在大肠癌中, Ets-1的表达与MMP-1和VEGF的表达呈正相关(r = 0.447, P<0.01; r = 0.425, P<0.05).

结论： Ets-1在大肠癌中高表达, 与临床分期、浸润深度、转移密切相关.Ets-1的表达与MMP-1和VEGF的表达呈正相关, 三者的表达水平可作为判定大肠癌恶性生物学行为的参考指标.

关键词：转录因子Ets–1; 基质金属蛋白酶–1; 血管内皮生长因子; 大肠癌

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0 引言

众所周知, 肿瘤的恶性生物学行为－侵袭转移是导致癌症患者死亡的主要原因, 研究证实, 肿瘤灶的血管生成加速了实体瘤的生长, 侵袭, 转移[1,2], Ets-1是与肿瘤血管发生和侵袭转移有关的转录因子[3,4]. 近来关于转录因子Ets-1在血管发生和浸润转移中的作用受到了国内外学者的关注[5-8], 但在大肠癌中关于Ets-1与MMP-1, VEGF的相关研究较少. 我们用免疫组化SP法检测Ets-1和MMP-1, VEGF在大肠癌中的表达水平及关系, 探讨Ets-1与大肠癌血管发生和浸润转移的关系, 为大肠癌的早期发现和判断预后提供理论依据.

1 材料和方法

1.1 *材料* 2003-10/2004-10手术切除大肠癌标本61例, 男30例, 女31例, 平均年龄52.6(26-81)岁, 肿瘤平均直径为5.5 cm. 病理组织学诊断高分化腺癌21例, 中分化腺癌28例, 低分化腺癌12例. Duke's A期14例, B期18例, C期17例, D期12例. 淋巴结转移29例, 未转移者32例. 远处转移12例, 未转移49例. 所有患者术前均未经过任何抗癌治疗. 另21例正常大肠组织为对照(取自肠镜标本). 标本均经40 g/L甲醛固定, 常规石蜡切片厚3-5 μm. 兔抗人Ets-1多克隆抗体购自美国Santa Cruz公司, 兔抗人MMP-1多克隆抗体和VEGF多克隆抗体购自武汉博士德生物工程有限公司, 即用型SP试剂盒和DAB显色剂购自北京中山试剂公司, 其他常规试剂均为国产分析纯试剂.

1.2 *方法* 采用免疫组化SP法染色, 每批染色均设立对照组, 以PBS代替一抗为阴性空白对照, 用已知阳性切片为阳性对照. 简要步骤如下: 组织切片常规脱蜡脱水后, 使用3 mL/L H_2O_2甲醇阻断内源性酶, 柠檬酸抗原修复液热水浴30 min, 用15 mL/L的正常山羊血清以减少非特异性着色, 再滴入相应抗体(Ets-1, MMP-1和VEGF的滴度均为1∶100), 4℃冰箱过夜, 继而滴入1∶200生物素标记的第二抗体, 30 min后清洗切片后再滴入1∶200稀释的链霉素抗生素蛋白-过氧化物酶(SP), 孵育20 min后经1 g/L DAB-H_2O_2显色后, 苏木素复染, 常规封片, 镜检并摄像. 细胞质出现棕黄色颗粒者为阳性, 高倍镜下(×200)对每张切片随机选择5个视野, 计数200个细胞/视野, 按阳性细胞数占视野总细胞数的百分比分为3级: 无阳性细胞或阳性细胞数<5%为阴性(-), 阳性细胞数在5-50%之间为阳性(+), 阳性细胞数>50%为强阳性(++).

统计学处理 采用SPSS11.0分析软件进行统计学处理, 根据数据性质, 分别应用χ^2检验, fishers精确概率法以及Spearman等级相关分析, 设P<0.05为差异显著性标准.

2 结果

2.1 Ets-1, VEGF和MMP-1的表达 Ets-1, MMP-1和VEGF在大肠癌中阳性率分别为75.4%, 78.7%和82.0%, 显著高于癌旁正常大肠黏膜(χ^2 = 18.983, P<0.01; χ^2 = 22.285, P<0.01; χ^2 = 23.963, P<0.01), Ets-1, MMP-1和VEGF在癌旁正常大肠黏膜中的表达均为阴性. Ets-1阳性染色颗粒以癌细胞胞质为主, 少数可见癌细胞胞核染色. MMP-1阳性染色颗粒以癌细胞胞质为主, 主要表达在侵袭前沿, 和Ets-1的表达是共定位的, 在部分间质细胞也可见阳性表达. VEGF阳性染色颗粒以癌细胞胞质为主, 少量可见癌细胞胞膜染色, 在部分血管内皮细胞可见阳性表达(图1).

2.2 Ets-1, VEGF和MMP-1的表达与临床病理的关系 Ets-1的表达与肿瘤大小和分化程度无关(P>0.05),与Duke's分期、浸润深度、淋巴结转移和远处转移相关(χ^2 = 10.718, P<0.01; χ^2 = 7.705, P<0.01; χ^2 = 9.333, P<0.01; χ^2 = 5.472, P<0.05). MMP-1的表达与肿瘤大小和分化程度无关(P>0.05),与Duke's分期、浸润深度、淋巴结转移和远处转移有关(χ^2 = 8.323, P<0.01; χ^2 = 19.101, P<0.01; χ^2 = 3.965, P<0.05; χ^2 = 4.125, P<0.05). VEGF的表达与肿瘤大小和分化程度无关(P>0.05), 与Duke's分期、浸润深度、淋巴结转移和远处转移有关(χ^2 = 6.145, P<0.05; χ^2 = 14.707, P<0.01; χ^2 = 4.638, P<0.05; χ^2 = 5.034, P<0.05, 表1).

2.3 Ets-1, MMP-1和VEGF的相互关系 在大肠癌中, Ets-1和MMP-1表达呈正相关(r = 0.447, P = 0.005), Ets-1表达和VEGF呈正相关(r = 0.425, P = 0.012, 表2).

3 讨论

肿瘤的生长和转移依赖于肿瘤血管形成.在新生血管形成之前, 由于被动供氧和营养扩散的限制, 肿瘤灶仅以一种小的, 无症状的病损存在. 而新生血管形成之后, 肿瘤灶局部快速播散, 增强肿瘤灶的远处转移能力[9-11]. 因此, 恶性肿瘤的生长转移与其间质血管的生成密切相关, 如果能找到有效调节血管生成的途径, 则有望控制肿瘤的生长和转移, 从而阻止肿瘤的恶性生

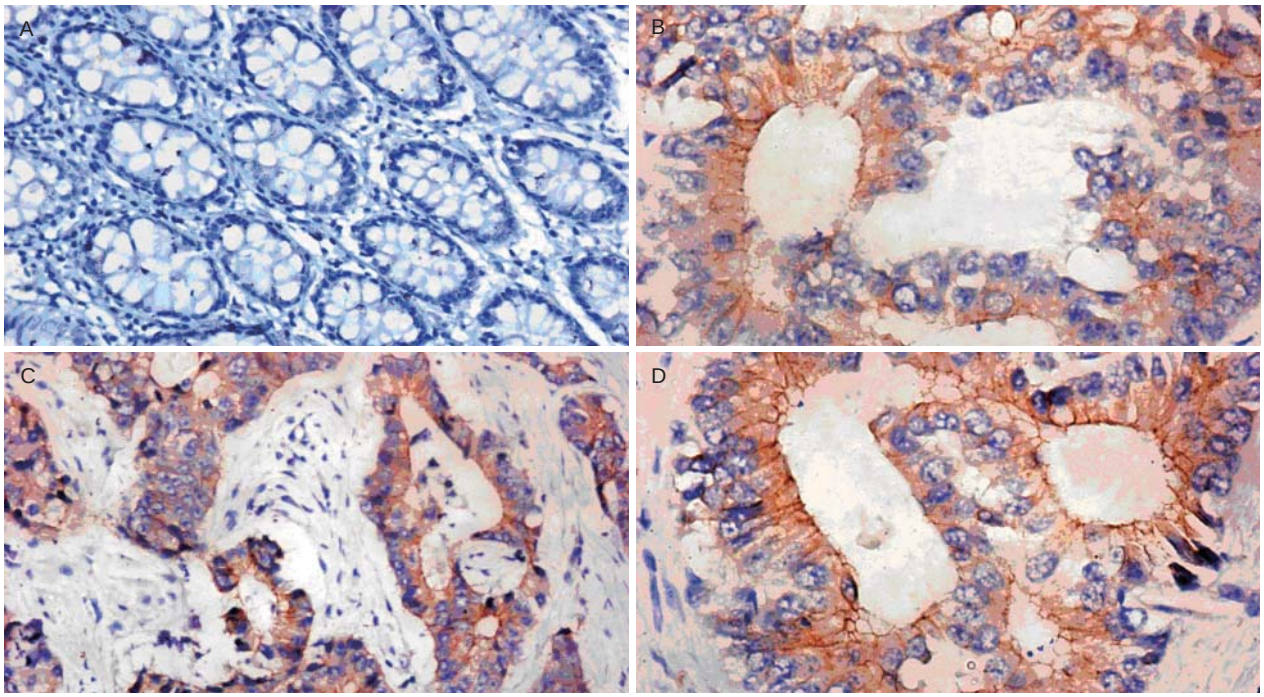

图 1 大肠癌组织中Ets-1，MMP-1和VEGF的表达. A：正常组织未见Ets-1的表达 (×200)；B：Ets-1在肿瘤细胞胞质中明显表达(×400)；C：MMP-1在肿瘤细胞胞质中明显表达 (×200)；D：VEGF在肿瘤细胞胞质中明显表达(×400).

物学行为, 延长肿瘤患者的生命. Ets-1是从白血病病毒E26分离出来的v-ets同源的原癌基因c-ets-1的表达产物, 它是Ets家族中具有代表性的转录因子. Ets家族是一组转录因子群, 具有由85个氨基酸构成的winged helix-turn-helix构造的DNA结合区(称作ETS区), 可以识别、结合嘌呤丰富的DNA核心序列GGAA/T, 这一序列存在于与细胞外基质降解以及血管生成有关的许多基因的5'-侧翼调节区, 如MMP-1, MMP-3, MMP-9和尿激酶型纤溶酶原激活物(uPA), 从而调节这些基因的转录[12-14]. Vandenbunder *et al*[15]用鸡胚进行原位杂交分析中发现, 血管形成(vasculogenesis)和血管新生(angiogenesis)时, 处于血管形成期的内皮细胞中都高表达Ets-1 mRNA. Khatun *et al*[16]发现Ets-1可以上调MMP-1, MMP-3, MMP-9, 整合素β和uPA的表达, 使内皮细胞转化为成血管表型, 从而诱导了癌组织的血管生成, 促进了癌的侵袭转移. 本研究发现, Ets-1在大肠癌中呈高表达, 有淋巴结和远处转移者Ets-1阳性表达率显著高于无淋巴结和无远处转移者, 且随着Duke's

表 1 Ets-1，MMP-1和VEGF的表达与大肠癌临床病理的关系

病理因素		*n*	Ets-1		MMP-1		VEGF	
			+	−	+	−	+	−
大小	≤5 cm	28	21	7	22	6	23	5
	>5 cm	33	25	8	26	7	27	6
组织学	高	21	15	6	15	6	16	5
分化	中	28	22	6	24	4	24	4
	低	12	9	3	9	3	10	2
Duke's	A	14	7	7	8	6	9	5
分期	B	18	12	6	13	5	14	4
	C	17	15	2	15	2	15	2
	D	12	12	0[b]	12	0[b]	12	0[a]
浸润	T1	5	2	3	1	4	2	3
深度	T2	9	5	4	4	5	5	4
	T3	15	11	4	13	4	12	3
	T4	32	28	4[b]	30	2[b]	31	1[b]
淋巴结	有	29	27	2	26	3	27	2
转移	无	32	19	13[b]	22	10[a]	23	9[a]
远处	有	12	12	0	12	0	12	0
转移	无	49	34	15[a]	36	13[a]	38	11[a]

[a]$P<0.05$, [b]$P<0.01$.

表 2 Ets-1, MMP-1和VEGF的相互关系

Ets-1的表达	MMP-1的表达		VEGF的表达	
	+	−	+	−
+	41	5	42	4
−	7	8	8	7

分期和浸润深度的进展, Ets-1的表达显著增加.

MMPs是一大类锌依赖性内肽酶家族, 活性部位都含有一个Zn^{2+}, 均能降解一种或几种细胞外基质, 在基质降解过程中起主导作用. MMP-1(亦称胶原酶)能降解Ⅰ, Ⅱ, Ⅲ型胶原, 把Ⅰ型胶原分解成1/4和3/4片段, 破坏基底膜, 通过对细胞外基质的改建, 促进肿瘤新生血管的形成, 利于肿瘤的浸润与转移[17-20]. 目前认为, 肿瘤侵袭转移的进程依赖于肿瘤细胞蛋白水解活性的增加[21]. 已知Ⅰ和Ⅲ型胶原是胃肠道间质的主要结构组分, 故MMP-1在降解肠道组织基底膜, 以利于肿瘤的进一步侵袭中起了重要作用[22]. 基因分析表明, MMPs的启动子区域PEA-3位点是Ets基因产物的结合点, 是一个功能性的转录元件[23]. 我们发现MMP-1主要表达在大肠癌细胞的胞质里, 且主要表达在侵袭前沿, 和Ets-1的表达是共定位的, 相关分析也显示Ets-1和MMP-1显著正相关, 从而表明Ets-1和MMP-1都在大肠癌的侵袭中起了重要作用. VEGF是目前引起大家关注的最主要的一种促血管生长的因子, 亦称血管渗透因子(vascular permeability factor, VPF)[24], 它是一个有效的, 多功能的细胞因子, 特异作用于血管内皮细胞, 促进内皮细胞的有丝分裂和趋化作用, 还增加血管通透性, 使管内的纤维蛋白原等外渗[25]. 在肿瘤细胞, VEGF通过直接刺激内皮细胞增殖和迁移发挥重要作用. 它也活化很多蛋白酶降解周围的基质, 促进肿瘤的侵袭转移[26]. Iwasaka *et al*[27]发现VEGF, bFGF可诱导内皮细胞表达Ets-1, 表达的Ets-1进一步诱导uPA, MMP-1等在血管新生中所必要的基因的表达. 另一方面, VEGF诱导产生的Ets-1可调节VEGFR-1(Flt-1)的表达, 从而促进VEGF与内皮细胞的结合[28]. 我们发现, VEGF与Ets-1的表达呈明显正相关, 支持VEGF诱导Ets-1基因表达的观点, 从而提出VEGF和Ets-1可能在血管发生中起协同作用.

Hahne *et al*[29]报道VEGF可诱导内皮细胞表达Ets-1基因, 而后者上调MMP-1, -3, -9和uPA等蛋白水解酶类的表达, 促使基底膜分解, 参与血管形成过程. 在这个通路中, Ets-1处于中间环节, 如果阻断Ets-1的表达则有可能达到阻断肿瘤血管生成的目的[30]. Kitange *et al*[31]报道, 用Ets-1的反义寡核苷酸处理神经胶质瘤细胞后, 可抑制细胞的迁移和侵入, 同时伴有Ets-1和uPA表达的下调. 应用Ets-1的反义寡核苷酸可有效抑制人内皮细胞和血管平滑肌细胞中VEGF, HGF和c-met的表达[32]. 提示Ets-1反义寡核苷酸有望成为一个有效的抗肿瘤药物.

总之, 本实验证实Ets-1在大肠癌中高表达, 与临床分期、浸润深度、转移密切相关, 在大肠癌血管发生和侵袭转移中都起了重要作用. Ets-1和MMP-1, VEGF均参与肿瘤浸润和淋巴转移过程, 检测三者的表达可做为判定大肠癌恶性生物学行为的参考指标, 为大肠癌的早期发现和判断预后提供理论依据.

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• 消息 •

更正与说明专栏

本刊讯 《世界华人消化杂志》为了对同行评议、编辑、校对、审读、文章价值等质量进行跟踪报道，特设“更正与说明”固定专栏，包括“事实纠错”、“文字更正”、“解释说明”三个子栏目，不仅对前一期或近期出现的文字差错和事实错误进行更正、就引发歧义或晦涩难懂之处做解释说明，而且针对文章的学术水平等进行讨论. 在此，我们热烈欢迎读者、作者、编委等积极审读《世界华人消化杂志》，给更正与说明栏目投稿. 投稿者凭文章的编号，可免费注册(http://www.wjgnet.com/1009-3079/new/39.doc)使用中国生物医学基金论文摘要库3年. 中国生物医学基金论文摘要库(http://www.wjgnet.com/cmfa/index.jsp)收录了1994-2005年国内发表在1204种生物医学类期刊总计20万以上的论文摘要. 这些论文受国家、军队和省部级自然科学基金、杰出青年基金、重大计划项目基金资助，内容丰富、数据准确，体现了我国生物医学的发展历程、脉络和方向，可为相关领域广大学者和研究人员了解并掌握当前研究动态、开辟新的研究领域提供思路. (世界胃肠病学杂志社 2005-10-10)