

原发性肝癌组织芯片中乙酰肝素酶的表达及意义

陈 罡, 党裔武, 罗殿中, 冯震博, 唐小玲

背景资料
乙酰肝素酶(HPA)是目前发现的能切割细胞外基质中硫酸肝素蛋白多糖侧链的内源性糖苷酶。HPA在肿瘤血管生成, 肿瘤生长浸润和转移中发挥重要的作用。组织芯片技术作为一项新兴的科研技术已被应用于肿瘤相关基因的科研工作中。

陈罡, 党裔武, 罗殿中, 冯震博, 唐小玲, 广西医科大学病理教研室 第一附属医院病理科 广西壮族自治区南宁市 530021
中国高等学校博士学科点专项科研基金项目资助, No. 20050598005
广西科学研究与技术开发计划应用基础研究项目资助, No. 0639040
通讯作者: 罗殿中, 530021, 广西壮族自治区南宁双拥路, 广西医科大学病理教研室, 广西医科大学第一附属医院病理科。
luodianzhong@yahoo.com.cn
电话: 0771-5356534 传真: 0771-5358502
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Expression of heparanase in tissue microarrays of primary hepatocellular carcinoma and its significance

Gang Chen, Yi-Wu Dang, Dian-Zhong Luo, Zhen-Bo Feng, Xiao-Ling Tang

Gang Chen, Yi-Wu Dang, Dian-Zhong Luo, Zhen-Bo Feng, Xiao-Ling Tang, Department of Pathology, Guangxi Medical University, Nanning 530021, Guangxi Zhuang Autonomous Region, China

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Correspondence to: Dian-Zhong Luo, Department of Pathology, Guangxi Medical University, Shuangyong Road, Nanjing 530021, Guangxi Zhuang Autonomous Region, China. luodianzhong@yahoo.com.cn

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Abstract

AIM: To investigate the expression of heparanase in tissue microarrays of hepatocellular carcinoma (HCC), and its clinical significance.

METHODS: Tissue microarrays comprised 125 tissues from HCC, 48 from tumor-adjacent liver, 62 from cirrhosis, and 23 from normal liver. Immunohistochemistry was employed to detect the expression of heparanase. Correlation between the expression and clinicopathological features of HCC was analyzed statistically.

RESULTS: The positive rate of HPA in HCC tissues (45.83%) was significantly higher than that in the adjacent-tumor liver (27.08%) ($\chi^2 = 2.23$, $P < 0.05$, cirrhosis (6.45%) ($\chi^2 = 5.262$, $P <$

0.05) and normal liver tissues (4.35%) ($\chi^2 = 3.895$, $P < 0.05$). Heparanase expression in tumor-adjacent tissues was significantly higher than that in cirrhosis ($\chi^2 = 2.882$, $P < 0.05$) and normal liver ($\chi^2 = 2.361$, $P < 0.05$). The rate of heparanase expression in HCC tissues in TNM stage I and II tumors was significantly lower than that in the stage III and IV tumors (29.41% vs 67.31%; $\chi^2 = 4.111$, $P < 0.05$); the rate of heparanase in cases without metastasis within 20 months was significantly lower than that in those with metastasis (14.71% vs 63.33%; $\chi^2 = 3.978$, $P < 0.05$). HPA expression in patients with AFP ≥ 400 $\mu\text{g/L}$ was 52.05%, 71.74% in portal vein tumor embolus, 73.91% in multiple tumor nodes, and 57.89% in tumors ≥ 5 cm diameter. This was significantly higher than in patients with AFP < 400 $\mu\text{g/L}$ (36.17%; $\chi^2 = 2.071$, $P < 0.05$), without tumor embolus (29.73%; $\chi^2 = 4.472$, $P < 0.05$), single tumor node (28.38%; $\chi^2 = 4.847$, $P < 0.05$), and tumor diameter < 5 cm (25%; $\chi^2 = 3.471$, $P < 0.05$). Heparanase expression was not associated with patient age, sex, histological classification, cirrhosis or tumor capsular infiltration.

CONCLUSION: Overexpression of heparanase plays an important role in the pathogenesis, development and metastases of HCC. The heparanase gene serves as an important molecular biological indicator in diagnosing and predicating the biological behavior of HCC patients.

Key Words: Heparanase; Carcinoma; Hepatocytes; Immunohistochemistry; Tissue microarrays

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摘要

目的: 探讨乙酰肝素酶(heparanase, HPA)蛋白在原发性肝细胞癌(HCC)组织芯片中的过度表达及临床意义。

方法: 125例HCC患者肝组织、48例肝癌患者

癌旁组织、62例肝硬化患者肝组织及23例肝血管瘤患者相应正常肝组织构建组织微阵列. 应用免疫组织化学检测HPA蛋白的表达水平, 并分析其与HCC临床病理特征的关系.

结果: HCC组织中的HPA蛋白的阳性率45.83%明显高于癌旁组织27.08% ($\chi^2 = 2.23$, $P < 0.05$), 肝硬化6.45% ($\chi^2 = 5.262$, $P < 0.05$)和正常肝组织4.35% ($\chi^2 = 3.895$, $P < 0.05$). 癌旁组织中的HPA蛋白阳性率明显高于肝硬化 ($\chi^2 = 2.882$, $P < 0.05$)及正常肝组织 ($\chi^2 = 2.361$, $P < 0.05$); HCC中临床TNM分期 I 期HPA阳性率明显低于 II 期 (29.41% vs 67.31%, $\chi^2 = 4.111$, $P < 0.05$); HCC中无转移组HPA阳性率明显低于转移组 (14.71% vs 63.33%, $\chi^2 = 3.978$, $P < 0.05$); HPA表达率在AFP ≥ 400 $\mu\text{g/L}$ 和AFP < 400 $\mu\text{g/L}$ 组 (52.05% vs 36.17%, $\chi^2 = 2.071$, $P < 0.05$)、有无门脉癌栓组 (71.74% vs 29.73%, $\chi^2 = 4.472$, $P < 0.05$)、多个和单个肿瘤结节组 (73.91% vs 28.38%, $\chi^2 = 4.847$, $P < 0.05$)以及肿瘤直径 ≥ 5 cm和 < 5 cm组 (57.89% vs 25%, $\chi^2 = 3.471$, $P < 0.01$)分别具有显著性意义. HPA表达与年龄、性别、分化程度、有无肝硬化及肿瘤包膜浸润无关.

结论: HPA高表达在HCC的发生、发展及转移中起重要作用. 检测HPA蛋白指标有助于HCC诊断和判断患者预后.

关键词: 乙酰肝素酶; 癌; 肝细胞; 免疫组织化学; 组织芯片

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0 引言

乙酰肝素酶(heparanase, HPA)是目前发现的哺乳动物细胞中唯一能切割细胞外基质中硫酸肝素蛋白多糖侧链的内源性糖苷酶. 研究发现HPA能加快血管生成, 促进肿瘤生长和转移, 其在多种肿瘤组织中呈现高表达状态^[1-5], 并且与肿瘤的侵袭性、转移性和复发关系密切^[6-10]. 组织芯片技术因为其高效快速等特点, 已被广泛应用于多种肿瘤相关基因的科研工作中^[11-15]. 为此, 我们采用组织芯片技术回顾性的检测了HPA蛋白在125例HCC患者肝组织, 48例癌患者癌旁组织和89例非癌患者肝组织中的表达及临床意义, 报道如下.

1 材料和方法

1.1 材料 2002-5/2005-12广西医科大学第一附属医院以及广西桂林临床病理诊断中心接受的HCC患者125例, 患者均为病理学检查证实. 有效例数120例, 男115例, 女5例, 年龄23-81(平均 49.2 ± 11.2)岁. HCC患者AFP阳性73例, 阴性47例. 术后均继续给予以化疗为主的综合治疗. 按照WHO的标准HCC分为: 高分化9例, 中分化73例, 低分化38例. 按国际TNM分期HCC分为: I 期15例, II 期53例, III期23例, IV期29例. 其中64例追踪20 mo, 转移复发情况由病理和临床决定, 转移复发30例, 无转移复发34例. 48例患者中癌旁肝组织为距癌结节2 cm以上的肝组织, 均为有效例数, 其中伴肝硬化36例, 无肝硬化12例. 非癌患者包括单纯性肝硬化及肝血管瘤患者, 其中单纯性肝硬化患者64例, 有效例数62例, 男41例, 女21例, 年龄15-74(平均 43.3 ± 12.6)岁. 25例肝血管瘤周围正常肝组织, 有效例数23例, 男16例, 女7例, 年龄18-72(平均 42.3 ± 11.2)岁. 抗HPA兔抗人多克隆抗体购于武汉博士德生物工程有限公司. 抗HPA兔单抗已知阳性胃癌组织切片作阳性对照, 以PBS代替一抗作阴性对照. 免疫组化二步法试剂盒(Polymer Detection System for Immuno-Histological Staining, PV-9000)为北京中杉金桥生物技术有限公司产品.

1.2 方法

1.2.1 组织芯片制作: 对供体组织苏木精-伊红(HE)染色切片作形态学观察, 并在供体蜡块上准确标记所需要的靶点. 参照Kallioniemi *et al*^[16]创建的方法, 利用组织芯片制作仪(Beecher)钻取靶点组织, 并转移至受体蜡块相应的孔位上, 制成所需的阵列蜡块. 每例取2处, 常规方法作4 μm 切片制作成组织芯片. HE染色, 确定组织芯片中的组织样本及形态学表现.

1.2.2 免疫组织化学检测: 4 μm 厚石蜡切片, 65℃烘烤脱蜡, 30 mL/L过氧化氢(H_2O_2)去离子水阻断内源性过氧化物酶10 min, 微波修复抗原, 加一抗37℃湿盒中孵育1 h, 加聚合体助手(Polymer Helper)37℃反应30 min, 加兔多抗(polyperoxidase-anti-rabbit)IgG 37℃处理30 min, 冲洗后加二氨基联苯胺(DAB)显色, 苏木素复染, 脱水、封片后在光镜下观察. 凡细胞质中出现明显棕黄色颗粒者为阳性细胞. 由两名病理医师采用双盲法阅片和评分, 采用双评分半定量法进行评分: 靶细胞阳性率 $< 25\%$ 为0分, 25%-50%为1分, 51%-75%为2分, $> 75\%$ 为3分. 显

研发前沿
本文应用组织芯片技术回顾性的检测了HPA蛋白在HCC患者肝组织、癌旁组织和非癌患者肝组织中的表达及临床意义, 探讨检测HPA蛋白指标对HCC诊断和判断患者预后方面的价值和意义.

相关报道

相关研究发现 HPA 在多种恶性肿瘤中异常高表达, 而相应的正常组织不表达或者低表达. Liu *et al* 的研究也发现, 肝癌组织 HPA 蛋白的表达显著高于癌旁肝组织及正常肝组织.

色程度按切片中细胞显色有无及染色深浅记分, 细胞无染色为0分, 浅棕黄色为1分, 棕黄色为2分, 棕褐色为3分. 将两分相加, <2分为(-), 2-3分为(+), 4-5分为(++), ≥6分为(+++).

统计学处理 应用SPSS13.0统计软件对数据进行 χ^2 检验, 以 $P<0.05$ 判为差异有显著性意义.

2 结果

成功制备了3个组织芯片腊块. 制作芯片过程中由于取材不当, 切片过程中组织折叠及染色过程中组织脱失, 最后HCC组有效率96%(120/125), 癌旁组100%(48/48), 非癌组95.51%(85/89), 总有效率96.56%(253/262). HPA蛋白阳性反应明显定位于胞质内, 为胞质内棕黄色颗粒状或斑片状染色, 阳性细胞的分布呈弥漫性、小巢状或散在分布. HCC组织中的HPA蛋白的阳性率明显高于癌旁、肝硬化及正常肝组织($P<0.05$, $P<0.01$, $P<0.01$). 癌旁组织中HPA蛋白阳性率明显高于肝硬化及正常肝组织($P<0.01$, $P<0.05$). HCC中临床TNM分期I、II期HPA阳性率明显低于III、IV期($P<0.01$). HCC中无转移组HPA阳性率明显低于转移组($P<0.01$). HPA表达率在AFP≥400 μg/L组、有门脉癌栓组、多个肿瘤结节组和肿瘤直径≥5 cm组分别明显高于AFP<400 μg/L组、无门脉癌栓组、单个肿瘤结节组和肿瘤直径<5 cm组($P<0.05$, 后三者均 $P<0.01$, 表1). HPA表达与患者年龄、性别、有无肝硬化、肿瘤分化程度、及肿瘤包膜浸润无关.

3 讨论

组织微阵列技术(tissue microarrays), 也称组织芯片(tissue chip)^[16-17], 具有体积小、高通量、经济、省时省力、易于重复、易于标准化、实验误差小和节约开支等优点^[18-22]. 我们制作了120例肝癌、48例癌旁及85例非癌患者的肝组织芯片. 芯片上样品排列整齐, 外形为圆形或类圆形, 较少皱折和掉片现象. 免疫组织化学染色定位准确, 结果判读明确, 组织芯片利用率达96.56%. 仅用几张芯片即完成了全部实验, 极大地节约了研究经费和降低了劳动量.

HPA基因定位于染色体4q21.3, cDNA全长1758 bp, 编码543个氨基酸^[23]. Hpa蛋白是由2条多肽链通过非共价结合形成的异二聚体, 相对分子质量分别为 8×10^3 kDa和 50×10^3 kDa, 他们共同来源于HPA蛋白前体^[24]. 人HPA共有6个

表1 HCC组织芯片中HPA表达与临床病理参数的关系

病理指标	n	HPA表达				χ ² 值	P值
		阳性(n)	阴性(n)	阳性率(%)			
组织							
HCC	120	55	65	45.83			
癌旁 ^a	48	13	35	27.08			
肝硬化 ^{bd}	62	4	58	6.45			
正常肝 ^{bc}	23	1	22	4.35			
年龄							
50	53	22	31	41.51	0.475	0.635	
<50	67	33	34	49.25			
性别							
男	115	53	62	46.09	0.266	0.790	
女	5	2	3	40.00			
分化程度							
高	9	5	4	55.56			
中	73	34	39	46.58			
低	38	16	22	42.11			
临床分期							
	68	20	48	29.41	4.111	0.000	
	52	35	17	67.31			
转移复发							
有	30	19	11	63.33	3.978	0.000	
无	34	5	29	14.71			
伴肝硬化							
有	36	9	27	25	0.557	0.578	
无	12	4	8	33.33			
AFP(μg/L)							
400	73	38	35	52.05	2.071	0.038	
<400	47	17	30	36.17			
门脉癌栓							
有	46	33	13	71.74	4.472	0.000	
无	74	22	52	29.73			
包膜浸润							
无包膜或包膜浸润	83	41	42	49.40	1.541	0.118	
包膜完整或无浸润	37	14	23	37.84			
肿瘤结节							
多个	46	34	12	73.91	4.847	0.000	
单个	74	21	53	28.38			
肿瘤直径(cm)							
5	76	44	32	57.89	3.471	0.001	
<5	44	11	33	25			

^a $P<0.05$, ^b $P<0.01$ vs HCC; ^c $P<0.05$, ^d $P<0.01$ vs 癌旁.

糖基化位点, HPA前体经糖基化后相对分子质量约为 65×10^3 kDa, 其糖基化与否对于酶活性并无明显影响. 在生理状态下, HPA主要分布在胎盘、脾脏、血小板以及中性粒细胞、单核细胞、T淋巴细胞和B淋巴细胞等免疫细胞内, 在

肝脏、肾脏及胰腺等均不表达. 研究发现HPA在多种恶性肿瘤中^[1-5]异常高表达, 而相应的正常组织不表达或者低表达. Liu *et al*^[30]的研究发现, 肝癌组织HPA蛋白的表达显著高于癌旁肝组织及正常肝组织, 与本实验结果相符, 说明HPA的表达可能与肝细胞的恶性转化及肿瘤的进展有关.

肿瘤细胞穿透基底膜及细胞外基质以及新生血管形成是肿瘤扩散和转移的基本过程. HPA作为一种葡萄糖醛酸内切酶, 通过切断硫酸乙酰肝素蛋白多糖(heparansulfate protoglycan, HSPGs)分子的侧链来降解细胞外基质和血管基底膜, 并能促使硫酸乙酰肝素结合型的生长因子(如bFGF和VEGF等)的释放和活化以诱导血管生成^[25-28], 从而促进肿瘤细胞的侵袭和转移. 多项研究结果表明HPA的高表达与肿瘤侵袭转移有极高相关性^[6-10,29]. Edovitsky *et al*^[31]使用RNA干扰技术阻断人乳腺癌细胞(MDA-MB-435)的HPA表达, 结果发现转染了特异性HPA siRNA在体外实验中侵袭和黏附都明显的减少. Goldshmidt *et al*^[32]将HPA转染到小鼠非转移性淋巴瘤细胞中, 发现细胞的侵袭性明显增强, 体内实验也证明转染HPA的小鼠更容易发生肝转移. Zhang *et al*^[6]使用反义寡核苷酸以及RNA干扰技术下调肝癌细胞系SMMC-7721的HPA表达后, 肝癌细胞的浸润和转移能力都降低. 以上研究均提示HPA与肿瘤的浸润转移关系密切. 本实验显示伴随转移的HCC癌组织中乙酰肝素酶的阳性率明显高于无转移组, 同时HPA表达率在有门脉癌栓组明显高于无门脉癌栓组, 提示HPA与代表肿瘤生物学行为的浸润转移因素有关. HPA高表达者, 易发生肿瘤细胞的浸润转移, 预后差.

本研究还发现, 临床TNM III、IV期HCC的HPA的表达明显高于I、II期, 说明HPA的表达与肿瘤的生长和进展有关, 临床分期越靠后, HPA的表达越高. 同时, HPA表达率在AFP \geq 400 μ g/L组、多个肿瘤结节组和肿瘤直径 \geq 5 cm组分别明显高于AFP $<$ 400 μ g/L组、单个肿瘤结节组和肿瘤直径 $<$ 5 cm组, 提示HPA的异常表达可能与HCC的恶性进展有关. HPA有望成为评价HCC预后的重要分子生物学检测指标和肝癌治疗的新靶点.

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应用要点
实验结果说明HPA高表达在HCC的发生、发展及转移中起作用, 检测HPA蛋白指标可能有助于HCC诊断和判断患者预后.

同行评价
本文方法成熟, 分析有据, 对基础和临床研究具有一定的指导意义和学术价值.

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编辑 李军亮 电编 郭海丽

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• 消息 •

世界华人消化杂志 2007 年 1 - 11 月份 收稿及发稿数字统计结果

本刊讯 世界华人消化杂志2007年1-11月份收稿及发稿数字统计结果: 自2007-01-01/2007-11-30, 世界华人消化杂志共收到稿件1450篇, 退稿585篇, 退稿率40.34%。发表文章707篇, 其中述评44篇(6.2%), 基础研究181篇(25.6%), 临床研究89篇(12.6%), 文献综述100篇(14.1%), 研究快报84篇(11.9%), 临床经验179篇(25.3%), 病例报告10篇(1.4%), 焦点论坛19篇(2.7%)。会议纪要1篇(0.14%), 英文摘要677篇(95.8%)。其中受国家级基金资助的157篇(22.2%), 省部级基金资助的222篇(31.4%)。作者分布遍及全国各地, 绝大多数来自高等院校及附属医院。(常务副总编辑: 张海宁 2007-11-15)