世界华人消化杂志®
wcjd@wjgnet.com
世界华人消化杂志 2010年7月18日; 18(20): 2117-2120
ISSN 1009-3079 CN 14-1260/R

文献综述 REVIEW

GP73与肝脏疾病关系的研究进展

李淑群, 陈 谦

李淑群, 陈谦, 桂林医学院附属医院肝胆外科 广西壮族自治区桂林市 541001
广西医疗卫生重点科研课题基金资助项目, No. 200883
作者贡献分布: 本文由李淑群综述, 陈谦审校.
通讯作者: 陈谦, 教授, 541001, 广西壮族自治区桂林市, 桂林医学院附属医院肝胆外科. qianchen98@yahoo.com
电话: 0773-2824373
收稿日期: 2010-04-09 修回日期: 2010-06-13
接受日期: 2010-06-22 在线出版日期: 2010-07-18

Advances in understanding the relationship between GP73 and hepatic diseases

Shu-Qun Li, Qian Chen

Shu-Qun Li, Qian Chen, Department of Hepatobiliary Surgery, the Affiliated Hospital of Guilin Medical College, Guilin 541001, Guangxi Zhuang Autonomous Region, China
Supported by: the Key Research Project Foundation of Guangxi Health Department, No. 200883
Correspondence to: Professor Qian Chen, Department of Hepatobiliary Surgery, the Affiliated Hospital of Guilin Medical College, Guilin 541001, Guangxi Zhuang Autonomous Region, China. qianchen98@yahoo.com
Received: 2010-04-09 Revised: 2010-06-13
Accepted: 2010-06-22 Published online: 2010-07-18

Abstract
Golgi protein-73 (GP73), a recently discovered Golgi glycoprotein localized on the membrane of the Golgi complex, is expressed in many types of human epithelial cells. In normal human liver, GP73 is highly expressed in biliary epithelial cells, but barely detectable in hepatocytes. However, GP73 expression has been found to be strongly up-regulated in hepatocytes and elevated in the serum in patients with liver diseases, especially those with hepatocellular carcinoma (HCC). Thus, GP73 is a candidate serum marker for the early detection of HCC.

Key Words: Golgi protein-73; Hepatocellular carcinoma; Early Diagnosis; Serum Marker

Li SQ, Chen Q. Advances in understanding the relationship between GP73 and hepatic diseases. Shijie Huaren Xiaohua Zazhi 2010; 18(20): 2117-2120

摘要
GP73(Golgi protein-73)是最近发现的一种高尔基体膜蛋白, 在正常人体多种组织中表达. 在正常肝脏中胆管上皮细胞呈高表达, 而肝细胞中几乎不表达, 但在多种肝脏疾病尤其是肝细胞癌中显著表达, 且其血清中明显升高. 因此, GP73可能是早期诊断肝细胞癌(hepatocellular carcinoma, HCC)的潜在血清肿瘤标志物.

关键词: 高尔基体蛋白73; 肝细胞癌; 早期诊断; 血清标志物

李淑群, 陈谦. GP73与肝脏疾病关系的研究进展. 世界华人消化杂志 2010; 18(20): 2117-2120
http://www.wjgnet.com/1009-3079/18/2117.asp

■背景资料
GP73是近年来发现的高尔基Ⅱ膜蛋白, 在多种肝脏疾病中显著升高, 尤其是肝细胞癌中, 对GP73的进一步研究有助于进一步揭示其与肝脏疾病尤其是肝细胞癌之间的关系.

0 引言
肝细胞癌(hepatocellular carcinoma, HCC)的增长速度之快已成为一个世界性难题, 其发病率在全球位居第4位, 总发患者数约56.4万[1]. 在我国, 由于乙型肝炎病毒(hepatitis B virus, HBV)携带者数量之庞大, 与此相关的HCC患者已占世界的55%左右, 其死亡率在恶性肿瘤中排第2位. 乙型肝炎、肝硬化及肝癌在医疗费用及社会负担中占有相当大的比重. 在过去相当长的时间里, 早期诊断HCC主要是依靠影像学手段及血清甲胎蛋白(alpha-fetoprotein, AFP), 但影像学检查对肿瘤体积较小者不易被发现; 临床上最常用的AFP也因其敏感性(39%-64%)不高并不令人满意[2]. 近年来研究发现多种物质如AFP-L3、磷脂酰肌醇蛋白聚糖3(glypican-3, GPC3)及肿瘤生长因子β(tumor growth factor-β, TGF-β)等可用于早期诊断HCC[3-10]. 其中高尔基体蛋白73(Golgi protein 73, GP73)被认为是最潜力的HCC血清标志物之一. 现将GP73的有关进展综述如下.

1 概述
GP73是Kladney等[11]在研究成人巨细胞性肝炎(giant-cell hepatitis, GCH)病原学时首次被发现的一种相对分子质量为7.3×10^4 Da的跨膜糖蛋白, 又称为Ⅱ型高尔基体膜蛋白(Golgi

■同行评议者
陈光, 教授, 吉林大学第一医院消化器官外科

■研发前沿
国内外多研究中心对不同种族、不同地域及不同生活习惯的相对大样本研究均表明, GP73有助于早期诊断HCC. 但GP73的具体生物学特性、是否可用于监测HCC的疗效及复发、阻断其表达是否可达到治疗HCC的目的等均需进一步深入研究.

phosphoprotein 2, Golph2)和高尔基体膜蛋白Ⅰ(Golgi membrane proteinⅠ, GolmⅠ). 业已证实, 编码GP73蛋白的基因位于第9号染色体, 全长共3 080个核苷酸, 编码区位于199-1 404 nt, 共编码402个氨基酸. GenBank目前已经公布了人类GP73序列共9条, 其长度和核苷酸序列都有不同.

已证实血浆中的可溶性GP73来源于高尔基体. 其富含酸性氨基酸, 氨基端为疏水末端, 主要位于高尔基体内, 构成跨膜区和信号肽切割位点. 羧基端位于高尔基体外, 包含有十四(烷)酰化连续序列(GLGNGRRS)、5个糖基化位点, 一个酸性结构域及一个卷曲螺旋结构, 但是到目前为止对这些结构的功能仍然不清[11-20]. 其转录调控机可能与下列因素有关: (1)体内HBV的复制; (2)血液中雌激素及骨化三醇水平; (3)肝硬化(与病原学无关); (4)血液中干扰素(interferin-γ, IFN-γ)和肿瘤坏死因子(tumor necrosis factor-α, TNF-α)含量; (5)机体内弗林含量的变化; (6)急慢性肝细胞损伤等[16,21-25].

2 GP73与肝脏疾病之间的关系

GP73在多种组织中均有表达, 但强弱不等. 在小肠、结肠以及胃中呈高表达, 而在心脏中表达最少, 在肝、肾、脾、肺、子宫及睾丸表达很弱但能检出. 在正常肝脏组织, GP73主要表达于胆管上皮细胞, 而在肝细胞则无表达或表达很少, 但是在有HBV及腺病毒感染的肝组织中, 胆管细胞表达GP73改变不明显, 而肝细胞则呈高表达[11,22,24,26].

2.1 GP73与肝良性疾病之间的关系 GP73的表达异常与肝脏多种疾病有关. 2000年Kladney等[11,23]首先发现在受到病毒感染后, 肝炎性多核细胞株表达GP73剧增, GP73 mRNA以及其蛋白在受到腺病毒感染后的HepG2细胞中表达. 而未受到感染的正常肝细胞几乎不表达. 后来其进一步证实各型肝硬化组织中几乎所有肝细胞均表达, 结缔组织周边和肝硬化结节尤甚. 同时发现在转染了HBV并且大量复制的HepG2215细胞株中高表达GP73, 而胆管细胞则无明显改变. 转染了HBV但无复制和未转染HBV的HepG2T14.1和HepG2细胞株中均无GP73表达. 后来Iftikhar等[25]证实这一结论并发现不同的病原学(HBV相关性肝炎、HCV相关性肝炎以及自身免疫性肝炎等)导致的肝炎患者中GP73的表达没有显著性差异, 随着病情的恢复, GP73表达水平也逐渐下降, GP73的水平与疾病的发展阶段有关而与其评分无关.

■相关报道
Mao等报道GP73在HCC患者血清中的表达明显高于其他肝良性疾病, 其诊断HCC的敏感性可达76.9%.

Wright等[27]比较了由Wilson病导致的肝损害和神经损害两组患者肝组织中GP73的表达情况, 结果阳性率明显不同(分别为79%和30%)并有统计学意义. 同时对缺失Wilson病基因的小鼠肝组织中GP73 mRNA的表达情况进行对比, 发现伴随着肝炎和肝硬化的发生, 其肝组织中GP73 mRNA水平明显升高, 但是在发生肝脏病变之前以及肝脏病变愈合之后虽然小鼠体内铜过量, 其组织中GP73 mRNA表达量均正常, 而痊愈后的肝硬化结节中GP73仍高, 由此得出在Wilson病肝细胞中GP73含量增高与铜超载无关, 主要是由肝脏的炎症、纤维化及发育不良所致.

2.2 GP73与HCC的关系 GP73的异常表达与肝细胞癌密切相关. Block等[28]科研小组首先用HBV感染土拔鼠建立HCC模型, 应用糖蛋白组学手段分析了患有HCC组和正常组血清中的蛋白表达差异, 结果发现HCC组血清中出现一个明显增强的FcA2G2组分, 进一步分析发现其代表了GP73组分, 从而推测其可能是HCC的重要肿瘤标志物, 并在HCC患者中的到证实. 同年5月, Schwegler等[29]应用表面增强激光吸收/电离飞行质谱(SELDI-TOF-MS)前瞻性分析了39例健康人、36例非肝硬化肝病患者、38例肝硬化患者以及57例HCC患者血清中蛋白表达差异, 并根据HCV阳性与否进一步分型, 结果提示肝病患者血清中蛋白表达水平与健康者明显不同, 且区分慢性丙型肝炎和丙型肝炎后肝癌的敏感性和特异性分别为61%和76%, 当与已知的血清标志物如AFP、DCP以及GPC3联合检测其敏感性和特异性可分别提高至75%和92%, 从而推测GP73有助于肝脏良恶性疾病的鉴别. 此后国外多项研究也证实HCC患者血清中GP73含量较其他疾病高且在HCC患者中, 且其敏感性较AFP高[30,31].

国内Mao等[32]用Western blot方法首先研究了25例HBV携带者, 24例HCC患者, 12例非肝病患者及99名健康人患者血清中GP73的量, 并且和血清中AFP含量进行比较, 发现肝癌患者血清中的GP73水平较乙肝携带者、非肝病患者及健康人显著提高, HBV携带者、非肝病患者及健康者之间没有显著性差异. 其诊断HCC的敏感性(76.9%)较AFP(48.6%)高且有统计学意义. 对HCC患者进行术后随访, 提示术后短期内(3-5 d)GP73水平没有下降, 而在术后的1.5-2

年其血清中GP73水平较术前明显下降. 随后Gu等[20]进行相对较大样本试验, 将29例HCC患者和其他肝病(57例乙型肝炎患者、69例肝硬化患者)及非肝脏疾病进行比较, 结果提示HCC患者血清中GP73水平远较其他肝病、其他非肝脏疾病及健康志愿者高, 以121 μg/L作为临界值, 其敏感性和特异性分别为72.4%和61.5%, 提出血清GP73可能作为诊断HCC的血清肿瘤标志物. 此后多项研究亦证实GP73有助于早期诊断HCC[33,34]. 而谭龙益等[15]通过克隆、表达及纯化GP73自制多克隆抗体, 建立双抗体夹心酶联免疫吸附法测定150例肝癌、120例其他肝病以及200名健康体检者血清中GP73水平, 得出的结论是其诊断肝癌的敏感性和特异性分别为44.5%和82.0%, 若将120例良性肝脏疾病患者加入对照组, 其敏感性和特异性分别降至43.3%和77.8%, 其敏感性和特异性与上述报道所有区别. 同时应用免疫组化技术观察各组标本, 结果也证实在正常肝组织中, 胆管细胞表达GP73水平较高, 而肝细胞表达水平很低. HCC患者肝组织标本中肝癌细胞表达GP73水平均增强, 且与血清学检测结果基本一致.

3 结论

HCC患者一旦发现基本上都为晚期. 被公认为“金标准”的血清学指标AFP已在全球范围内广泛应用于普查、诊断、疗效判断及复发监测, 但其敏感性不高, 且有报道认为在其他疾病中亦有升高. GP73作为早期诊断HCC的潜在血清肿瘤标志物和我国肝癌高危险人群的庞大基数, 使GP73研究对降低我国HCC病死率有着尤为重要的意义, 多项研究证实其在HCC患者血清中升高, 同时也有相关研究报道, 在其他疾病中也有升高, 如小细胞性肺癌、肾癌及前列腺癌等[35-41], 使其特异性受到限制. 目前对GP73的分子生物学特性尚知之甚少, 如其蛋白上各结构域的具体功能如何、通过何种调控使其表达量增加、通过何种机制剪切并使其转运至细胞膜外、GP73在肝细胞受到损害及HCC患者中升高的原因及机制是否相同、其表达量上升是否可促进肿瘤的发生与发展、是否可用于HCC患者疗效判断及复发监测、通过阻断其表达是否可达到治疗HCC的目的等均未明. 其复杂性及研究的局限性离临床还很远, 实用性还有待进一步深入研究.

4 参考文献

1 Jemal A, Siegel R, Ward E, Hao Y, Xu J, Murray T, Thun MJ. Cancer statistics, 2008. *CA Cancer J Clin* 2008; 58: 71-96

2 徐海峰, 杨华渝, 张宏冰, 毛一雷. 改变肝癌早期诊断和治疗现状的新肝癌血清标志物. 基础医学与临床 2008; 28: 104-108

3 吴玮, 姚登福, 顾丽华, 樊翼伟, 陆秀凤, 李小华, 邱历伟, 吴信华. 亲和层析微柱法测定肝癌特异性AFP. 临床检验杂志 2006; 24: 10-12

4 Dong ZZ, Yao DF, Yao M, Qiu LW, Zong L, Wu W, Wu XH, Yao DB, Meng XY. Clinical impact of plasma TGF-beta1 and circulating TGF-beta1 mRNA in diagnosis of hepatocellular carcinoma. *Hepatobiliary Pancreat Dis Int* 2008; 7: 288-295

5 Yoon SK. Recent advances in tumor markers of human hepatocellular carcinoma. *Intervirology* 2008; 51 Suppl 1: 34-41

6 Porta C, De Amici M, Quaglini S, Paglino C, Tagliani F, Boncimino A, Moratti R, Corazza GR. Circulating interleukin-6 as a tumor marker for hepatocellular carcinoma. *Ann Oncol* 2008; 19: 353-358

7 Zhou L, Liu J, Luo F. Serum tumor markers for detection of hepatocellular carcinoma. *World J Gastroenterol* 2006; 12: 1175-1181

8 Khien VV, Mao HV, Chinh TT, Ha PT, Bang MH, Lac BV, Hop TV, Tuan NA, Don LV, Taketa K, Satomura S. Clinical evaluation of lentil lectin-reactive alpha-fetoprotein-L3 in histology-proven hepatocellular carcinoma. *Int J Biol Markers* 2001; 16: 105-111

9 Leerapun A, Suravarapu SV, Bida JP, Clark RJ, Sanders EL, Mettler TA, Stadheim LM, Aderca I, Moser CD, Nagorney DM, LaRusso NF, de Groen PC, Menon KV, Lazaridis KN, Gores GJ, Charlton MR, Roberts RO, Therneau TM, Katzmann JA, Roberts LR. The utility of Lens culinaris agglutinin-reactive alpha-fetoprotein in the diagnosis of hepatocellular carcinoma: evaluation in a United States referral population. *Clin Gastroenterol Hepatol* 2007; 5: 394-402; quiz 267

10 Montaser LM, Abbas OM, Saltah AM, Waked IA. Circulating AFP mRNA as a Possible Indicator of Hematogenous Spread of HCC Cells: A Possible Association with HBV Infection. *J Egypt Natl Canc Inst* 2007; 19: 48-60

11 Kladney RD, Bulla GA, Guo L, Mason AL, Tollefson AE, Simon DJ, Koutoubi Z, Fimmel CJ. GP73, a novel Golgi-localized protein upregulated by viral infection. *Gene* 2000; 249: 53-65

12 Puri S, Bachert C, Fimmel CJ, Linstedt AD. Cycling of early Golgi proteins via the cell surface and endosomes upon lumenal pH disruption. *Traffic* 2002; 3: 641-653

13 Natarajan R, Linstedt AD. A cycling cis-Golgi protein mediates endosome-to-Golgi traffic. *Mol Biol Cell* 2004; 15: 4798-4806

14 Beard M, Satoh A, Shorter J, Warren G. A cryptic Rab1-binding site in the p115 tethering protein. *J Biol Chem* 2005; 280: 25840-25848

15 谭龙益, 陈洁, 王皓. 血清II型高尔基体膜蛋白与人类肝细胞癌的关系. 中华肝脏病杂志 2009; 17: 288-291

16 Norton PA, Comunale MA, Krakover J, Rodemich L, Pirog N, D'Amelio A, Philip R, Mehta AS, Block TM. N-linked glycosylation of the liver cancer biomarker GP73. *J Cell Biochem* 2008; 104: 136-149

17 Bachert C, Fimmel C, Linstedt AD. Endosomal trafficking and proprotein convertase cleavage of cis Golgi protein GP73 produces marker for

■创新盘点

本文首次较全面地综述了有关GP73与肝脏疾病之间的关系, 尤其是与HCC之间的关系.

■同行评价
本文选题较新, 思路清晰, 对于肝细胞癌的早期诊断有一定的价值.

hepatocellular carcinoma. *Traffic* 2007; 8: 1415-1423
18 Moggs JG, Ashby J, Tinwell H, Lim FL, Moore DJ, Kimber I, Orphanides G. The need to decide if all estrogens are intrinsically similar. *Environ Health Perspect* 2004; 112: 1137-1142
19 Wang TT, Tavera-Mendoza LE, Laperriere D, Libby E, MacLeod NB, Nagai Y, Bourdeau V, Konstorum A, Lallemant B, Zhang R, Mader S, White JH. Large-scale in silico and microarray-based identification of direct 1,25-dihydroxyvitamin D3 target genes. *Mol Endocrinol* 2005; 19: 2685-2695
20 Gu Y, Chen W, Zhao Y, Chen L, Peng T. Quantitative analysis of elevated serum Golgi protein-73 expression in patients with liver diseases. *Ann Clin Biochem* 2009; 46: 38-43
21 谢红彬, 宫钰, 彭涛. 高尔基体驻膜糖蛋白GP73启动子克隆. 农业科学与技术(英文版) 2008; 9: 39-42, 136
22 Wright LM, Yong S, Picken MM, Rockey D, Fimmel CJ. Decreased survival and hepato-renal pathology in mice with C-terminally truncated GP73 (GOLPH2). *Int J Clin Exp Pathol* 2009; 2: 34-47
23 Kladney RD, Cui X, Bulla GA, Brunt EM, Fimmel CJ. Expression of GP73, a resident Golgi membrane protein, in viral and nonviral liver disease. *Hepatology* 2002; 35: 1431-1440
24 Kladney RD, Tollefson AE, Wold WS, Fimmel CJ. Upregulation of the Golgi protein GP73 by adenovirus infection requires the E1A CtBP interaction domain. *Virology* 2002; 301: 236-246
25 Iftikhar R, Kladney RD, Havlioglu N, Schmitt-Gräff A, Gusmirovic I, Solomon H, Luxon BA, Bacon BR, Fimmel CJ. Disease- and cell-specific expression of GP73 in human liver disease. *Am J Gastroenterol* 2004; 99: 1087-1095
26 Maitra A, Thuluvath PJ. GP73 and liver disease: a (Golgi) complex enigma. *Am J Gastroenterol* 2004; 99: 1096-1098
27 Wright LM, Huster D, Lutsenko S, Wrba F, Ferenci P, Fimmel CJ. Hepatocyte GP73 expression in Wilson disease. *J Hepatol* 2009; 51: 557-564
28 Block TM, Comunale MA, Lowman M, Steel LF, Romano PR, Fimmel C, Tennant BC, London WT, Evans AA, Blumberg BS, Dwek RA, Mattu TS, Mehta AS. Use of targeted glycoproteomics to identify serum glycoproteins that correlate with liver cancer in woodchucks and humans. *Proc Natl Acad Sci U S A* 2005; 102: 779-784
29 Schwegler EE, Cazares L, Steel LF, Adam BL, Johnson DA, Semmes OJ, Block TM, Marrero JA, Drake RR. SELDI-TOF MS profiling of serum for detection of the progression of chronic hepatitis C to hepatocellular carcinoma. *Hepatology* 2005; 41: 634-642
30 Marrero JA, Romano PR, Nikolaeva O, Steel L, Mehta A, Fimmel CJ, Comunale MA, D'Amelio A, Lok AS, Block TM. GP73, a resident Golgi glycoprotein, is a novel serum marker for hepatocellular carcinoma. *J Hepatol* 2005; 43: 1007-1012
31 Riener MO, Stenner F, Liewen H, Soll C, Breitenstein S, Pestalozzi BC, Samaras P, Probst-Hensch N, Hellerbrand C, Müllhaupt B, Clavien PA, Bahra M, Neuhaus P, Wild P, Fritzsche F, Moch H, Jochum W, Kristiansen G. Golgi phosphoprotein 2 (GOLPH2) expression in liver tumors and its value as a serum marker in hepatocellular carcinomas. *Hepatology* 2009; 49: 1602-1609
32 Mao YL, Yang HY, Xu HF, Sang XT, Lu X, Yang ZY, Zhang JC, Zhong SX, Huang JF, Zhang HB. [Significance of Golgi glycoprotein 73, a new tumor marker in diagnosis of hepatocellular carcinoma: a primary study] *Zhonghua Yixue Zazhi* 2008; 88: 948-951
33 Hu JS, Wu DW, Liang S, Miao XY. GP73, a resident Golgi glycoprotein, is sensibility and specificity for hepatocellular carcinoma of diagnosis in a hepatitis B-endemic Asian population. *Med Oncol* 2010; 27: 339-345
34 李利军, 李新丰, 王高峰. GP73联合AFP、VEGF检测对原发性肝癌的诊断价值. 世界华人消化杂志 2009; 17: 3056-3060
35 Kristiansen G, Fritzsche FR, Wassermann K, Jäger C, Tölls A, Lein M, Stephan C, Jung K, Pilarsky C, Dietel M, Moch H. GOLPH2 protein expression as a novel tissue biomarker for prostate cancer: implications for tissue-based diagnostics. *Br J Cancer* 2008; 99: 939-948
36 Varambally S, Laxman B, Mehra R, Cao Q, Dhanasekaran SM, Tomlins SA, Granger J, Vellaichamy A, Sreekumar A, Yu J, Gu W, Shen R, Ghosh D, Wright LM, Kladney RD, Kuefer R, Rubin MA, Fimmel CJ, Chinnaiyan AM. Golgi protein GOLM1 is a tissue and urine biomarker of prostate cancer. *Neoplasia* 2008; 10: 1285-1294
37 Katada T, Ishiguro H, Kimura M, Mitui A, Harata K, Ogawa R, Kuwabara Y. GP73 contributes to the sensitivity of cisplatin in esophageal cancer. *Esophagus* 2009; 6: 173-176
38 Fritzsche FR, Kristiansen G, Riener MO, Dietel M, Oelrich B. GOLPH2 expression may serve as diagnostic marker in seminomas. *BMC Urol* 2010; 10: 4
39 Rosell R, Lord RV, Taron M, Reguart N. DNA repair and cisplatin resistance in non-small-cell lung cancer. *Lung Cancer* 2002; 38: 217-227
40 Fritzsche FR, Riener MO, Dietel M, Moch H, Jung K, Kristiansen G. GOLPH2 expression in renal cell cancer. *BMC Urol* 2008; 8: 15
41 Wei S, Dunn TA, Isaacs WB, De Marzo AM, Luo J. GOLPH2 and MYO6: putative prostate cancer markers localized to the Golgi apparatus. *Prostate* 2008; 68: 1387-1395

编辑 李军亮 电编 何基才