

血清甲胎蛋白、白细胞介素-6和高尔基体蛋白73在肝脏疾病中的表达特点及其对肝细胞癌的诊断价值

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【摘要】目的 探讨血清甲胎蛋白(AFP)、白细胞介素-6(IL-6)和高尔基体蛋白73(GP73)在肝病中的表达特点及对HBV相关原发性肝癌(PHC)的临床诊断价值。**方法** 选择2015年1月至2016年3月于解放军第一八〇医院肝病中心住院的慢性HBV感染者共391例为研究对象,采用全自动电化学发光免疫分析仪和酶联免疫法分别检测患者血清AFP、IL-6与GP73的表达水平,分析这3种血清标志物对PHC的诊断价值。**结果** CHB、乙型肝炎肝硬化(HLC)、PHC三组人群中,血清IL-6和GP73水平随病情加重而逐渐升高(P 均 < 0.05),失代偿期HLC组血清IL-6和GP73水平显著高于代偿期组(P 均 < 0.001),AFP表达水平于PHC II期、III期患者中显著升高($Z = 3.305$ 、 $P = 0.001$, $Z = 2.902$ 、 $P = 0.003$),血清IL-6和GP73水平随肝细胞癌等级升高而升高(P 均 < 0.05)。血清IL-6与GP73呈对数正相关($r = 0.553$, $P < 0.001$)。3种血清标志物诊断PHC的曲线下面积分别为0.788、0.787和0.649。AFP + IL-6联合患者组曲线下面积为0.873,敏感性显著升高,与AFP相比差异具有统计学意义($\chi^2 = 49.891$ 、 $P < 0.001$)。AFP + IL-6 + GP73联合组与AFP + IL-6联合组诊断价值差异无统计学意义($Z = 1.256$ 、 $P = 0.209$)。IL-6与GP73对失代偿期肝硬化和肝细胞癌的鉴别诊断价值不高,曲线下面积均低于0.6。**结论** IL-6可作为AFP诊断肝癌的补充预测因子,而GP73对肝癌的诊断价值不高。

【关键词】 失代偿期肝硬化; 肝癌; 甲胎蛋白; 白细胞介素-6; 高尔基体蛋白73

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【Abstract】Objective To investigate the pattern of serum α -fetal protein (AFP), interleukin-6 (IL-6) and Golgi protein 73 (GP73) expressed in liver diseases and the diagnostic value on hepatitis B virus related primary hepatic carcinoma (PHC). **Methods** Total of 391 patients with HBV in the 180th Hospital of PLA, from January 2015 to March 2016 were collected. AFP and IL-6 were detected by automatic electrochemical luminescence immunity analyzer. GP73 was detected by ELISA. Their diagnostic value for the PHC were analyzed by ROC analysis. **Results** Among chronic hepatitis B (CHB) group, HLC group and PHC group, the level of serum IL-6 and GP73 significantly increased when the disease worsened ($P < 0.05$). Compared with the compensated HLC group, the serum level of them showed higher in decompensated group ($P < 0.001$). The expression of AFP were significantly increased in stage II and III of PHC compared with stage I ($Z = 3.305$, $P = 0.001$; $Z = 2.902$, $P = 0.003$). The level of serum IL-6 and GP73 significantly increased when the stage of PHC rising ($P < 0.05$). There was positive logarithmic correlation between IL-6 and GP73 ($r = 0.553$,

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$P < 0.001$). The area under the ROC curve of AFP, IL-6 and GP73 for diagnosing PHC were 0.788, 0.787 and 0.649, respectively. When taking AFP and IL-6 as predictors together, the area was 0.873 and the sensitivity was significantly higher than AFP ($\chi^2 = 49.891$, $P < 0.001$). There was no difference between combined group of AFP + IL-6 + GP73 and AFP + IL-6 in diagnosing PHC ($Z = 1.256$, $P = 0.209$). IL-6 and GP73 could not distinguish decompensated HLC from hepatocellular carcinoma, their area under the ROC curve were both less than 0.6. **Conclusions** AFP and IL-6 could serve as a complementary factor to predict the occurrence of PHC, while the value of GP73 in diagnosing PHC was not high.

【Key words】Decompensated hepatic B liver cirrhosis; Hepatocellular carcinoma; α -fetal protein; Interleukin 6; Golgi protein 73

慢性乙型肝炎(chronic hepatitis B, CHB)是一种慢性炎症疾病,免疫应答是影响HBV感染结局的关键因素。病毒感染能刺激多种细胞分泌前炎症因子白细胞介素6(interleukin 6, IL-6), IL-6启动预警信号给免疫系统,激活体内免疫反应^[1]。多种数据表明CHB患者、进展性肝病患者IL-6表达显著高于健康人群,高水平的IL-6可能反映肝细胞坏死性炎症程度,且与慢性HBV感染者的病情加重有关^[2-3]。同时,IL-6参与的TLRs-MyD88-NF- κ B-IL-6信号途径于肝脏肿瘤的生成过程中发挥了关键作用^[4]。高尔基体蛋白73(Golgi protein 73, GP73)是高尔基体上的II型跨膜蛋白,于正常组织中表达量低,仅在胆管上皮细胞中有所表达,但在发生病变的肝细胞中表达显著上调^[5]。血清GP73水平可能与HBV感染者肝脏炎症损伤程度和免疫状态有关^[6-7],由于在肝癌患者中亦观察到GP73表达异常升高^[8],故一直作为有潜力的肝癌血清标志物被广泛研究。

IL-6与GP73均参与了慢性肝病的炎症反应,也影响慢性肝病的最终结局,本文旨在探讨二者在慢性HBV感染者中的表达特点、相互关系及对肝癌的诊断价值,现报道如下。

资料与方法

一、研究对象

收集2015年1月至2016年3月于解放军第一八〇医院肝病中心住院的慢性HBV感染者共391例,其中男性301例(76.98%),女性90例(23.02%);CHB患者140例,乙型肝炎肝硬化(hepatic B liver cirrhosis, HLC)129例(包括代偿期患者33例,失代偿期患者96例),HBV相关原发性肝癌(primary hepatic carcinoma, PHC)患

者122例,按国际抗癌联盟(union for international cancer control, UICC)颁布的肿瘤淋巴结转移(tumor node metastases, TNM)分期方法(2010年版)^[9]对肝癌进行分期,包括I期患者9例,II期患者48例,III期患者65例,平均年龄为(44 ± 15)岁,诊断标准均符合2015年修订的《慢性乙型肝炎防治指南(2015年版)》和2011年美国修订制定的《原发性肝细胞癌管理指南》^[10-11]。排除由甲、丙、丁、戊型病毒性肝炎或其他原因导致的肝功能损伤。标本均为新鲜分离血清, $-80\text{ }^{\circ}\text{C}$ 保存、整批待检。所有患者均签署知情同意书,本研究经医院伦理委员会批准。

二、检测方法

AFP与IL-6检测采用瑞士罗氏e601全自动电化学发光免疫分析仪与配套试剂测定。GP73测定,按照北京热景生物技术公司提供的GP73酶联免疫定量检测试剂盒说明书操作:每孔加入20 μl 血清标本和50 μl 稀释液,轻轻震荡混匀。封板置37 $^{\circ}\text{C}$ 温箱温育60 min。每孔加入酶标试剂100 μl ,封板后置37 $^{\circ}\text{C}$ 温箱温育30 min。洗板5次后扣干,加入显色剂A、B液各50 μl ,37 $^{\circ}\text{C}$ 避光显色15 min,每孔加入50 μl 终止液,10 min内上酶标仪(美国BIORAD-860酶标仪)检测。

三、统计学处理

采用SPSS 17.0、MedCalc 15.6软件进行统计分析,患者血清GP73水平呈近似正态分布,以 $\bar{x} \pm s$ 表示,AFP、IL-6呈偏态分布,采用中位数(四分位间距)[M(QR)]表示,应用MedCalc 15.10统计软件进行受试者操作特征(receiver operator characteristic, ROC)曲线分析,根据诊断试验评价的四格表,计算出最佳临界值、敏感性、特异性、准确性等^[12]。相关性分析采用Pearson法,两组均数比较采用 t 检验,中位数比较采用秩和检验,最佳

临界值、敏感性等比较采用Z检验、 χ^2 检验,以 $P < 0.05$ 为差异具有统计学意义。

结 果

一、CHB、HLC和PHC患者血清AFP、IL-6和GP73表达水平

CHB、HLC和PHC三组患者中,血清IL-6和GP73水平随病情加重而逐渐升高(P 均 < 0.05),PHC组患者血清AFP水平显著高于HLC和CHB组(P

均 < 0.001),见表1。失代偿期的肝硬化患者血清IL-6、GP73水平显著高于代偿期,与I期PHC患者相比,II期、III期PHC患者的AFP水平显著升高,但II期和III期PHC患者间AFP水平差异无统计学意义。另外,在PHC患者中,血清GP73和IL-6水平随着肝癌等级升高而升高(P 均 < 0.05),详见表2。

二、血清IL-6与GP73的相关性分析

入选的391例患者中,血清IL-6与GP73呈对数相关($r = 0.553$, $P < 0.001$),相关关系为 $\ln(GP73) = 4.364 + 0.248 \times \ln(IL-6)$,见图1。

表1 血清AFP、IL-6和GP73在不同肝脏疾病患者中的表达

组别	例数	AFP[M(QR), ng/ml]	IL-6[M(QR), pg/ml]	GP73($\bar{x} \pm s$, ng/ml)
CHB患者	140	4.91(12.37)	2.03(32.77)	114.20 ± 73.94
HLC患者	129	5.10(13.52)	11.07(25.31)	180.20 ± 90.32
PHC患者	122	193.90(9 762.08)	26.90(60.96)	204.00 ± 113.70
^a 统计量		$Z = 0.147$	$Z = 9.653$	$t = 6.573$
^a P		0.883	< 0.001	< 0.001
^b 统计量		$Z = 8.081$	$Z = 11.977$	$t = 8.465$
^b P		< 0.001	< 0.001	< 0.001
^c 统计量		$Z = 7.820$	$Z = 4.691$	$t = 1.849$
^c P		< 0.001	< 0.001	0.048

注: ^aHLC患者 vs. CHB患者; ^bPHC患者 vs. CHB患者; ^cPHC患者 vs. HLC患者

表2 血清AFP、IL-6和GP73在HLC患者与PHC患者中的表达

组别	例数	AFP[M(QR), ng/ml]	IL-6[M(QR), pg/ml]	GP73($\bar{x} \pm s$, ng/ml)
HLC患者				
代偿期	33	6.12(17.77)	2.76(92.30)	129.70 ± 77.55
失代偿期	96	5.02(11.80)	13.95(453.86)	197.50 ± 88.19
PHC患者				
I期	9	2.64(18.24)	7.47(112.81)	129.00 ± 78.22
II期	48	219.90(6 468.93)	10.39(1 263.67)	162.80 ± 98.59
III期	65	240.90(25 751.20)	39.59(730.51)	244.80 ± 113.00
^a 统计量		$Z = 1.400$	$Z = 4.984$	$t = 3.923$
^a P		0.161	< 0.001	< 0.001
^b 统计量		$Z = 3.305$	$Z = 1.852$	$t = 1.969$
^b P		0.001	0.044	0.037
^c 统计量		$Z = 2.902$	$Z = 2.109$	$t = 2.966$
^c P		0.003	0.035	0.004
^d 统计量		$Z = 0.168$	$Z = 3.351$	$t = 4.020$
^d P		0.866	< 0.001	< 0.001

注: ^a: 失代偿期HLC患者 vs. 代偿期HLC患者; ^b: PHC II期患者 vs. PHC I期患者; ^c: PHC III期患者 vs. PHC I期患者; ^d: PHC III期患者 vs. PHC II期患者

三、血清AFP、IL-6和GP73单独或联合检测对PHC的诊断价值分析

血清AFP、IL-6和GP73诊断PHC的曲线下面积分别为0.788、0.787和0.649（与ROC = 0.5相比， P 均 < 0.001 ）。AFP的特异性和准确性最高，分别为94.05%和83.12%，IL-6的敏感性最高（为84.43%），但特异性较低（为63.57%）。GP73的敏感性（40.98%）最差，特异性（81.04%）显著优于IL-6（ $\chi^2 = 29.577$ 、 $P < 0.001$ ）。AFP + IL-6联合患者组曲线下面积为0.873，敏感性优于AFP单独检测组（ $\chi^2 = 49.891$ 、 $P < 0.001$ ），特异性、准确性低于AFP（ $\chi^2 = 53.905$ 、 $P < 0.001$ ， $\chi^2 = 4.257$ 、 $P = 0.039$ ）。AFP + IL-6 + GP73联合患者组，曲线下面积为0.881，与AFP + IL-6联合患者组差异无统计学意义（ $Z = 1.256$ 、 $P = 0.209$ ），敏感性较AFP + IL-6联合组低（ $\chi^2 = 5.170$ 、 $P = 0.023$ ），特异性较AFP + IL-6联合组高（ $\chi^2 =$

12.339、 $P < 0.001$ ），准确性与两种联合组差异无统计学意义（ $\chi^2 = 2.850$ 、 $P = 0.091$ ）。

四、血清AFP、IL-6和GP73对失代偿期HLC与PHC的鉴别诊断价值分析

血清IL-6和GP73对失代偿期HLC、PHC的鉴别诊断价值不高，曲线下面积均 < 0.6 。AFP相对较好，敏感性、特异性和准确性均较高（与IL-6、GP73相比， P 均 < 0.001 ）。

讨 论

HBV感染呈世界性流行趋势，每年约60万人死于急性或慢性HBV感染。而我国又是慢性乙型肝炎的高流行区，现有CHB患者约2 000万例，其中25%~40%最终可进展为肝硬化或PHC，慢性HBV感染已成为潜在的威胁人类生命健康的全球公共卫生问题之一^[13]。

病毒、免疫应答和基因多态性是影响HBV感染结局的3个主要因素^[14-15]。HBV X蛋白（HBx）感染肝细胞时，能通过NF- κ B途径上调IL-6表达，而IL-6可促进肝细胞损伤和肝细胞的代偿性增生，IL-6还参与肝硬化患者肝星状细胞的增殖，与肝细胞的纤维化反应有关^[16-18]，持续性暴露在高水平的IL-6中能导致肝脏损伤最终导致肝癌^[19]。GP73表达不仅在HBV感染者中升高，在其他肝病，如丙型肝炎、自身免疫性肝炎和酒精性肝硬化等，也观察到了GP73表达异常增高^[20]，而许正据等^[6-7]研究表明，GP73与乙型肝炎患者病情严重程度呈

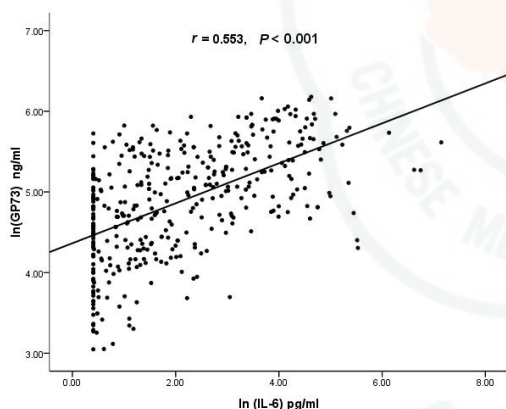


图1 血清IL-6与GP73的相关性

表3 AFP、GP73 和 IL-6 对 PHC 的诊断价值分析

标志物	AUC	Z值	^a P值	临界值	敏感性 (%)	特异性 (%)	准确性 (%)
AFP	0.788	10.041	< 0.001	84.77 ng/ml	59.02	94.05	83.12
IL-6	0.787	12.156	< 0.001	5.58 pg/ml	84.43	63.57	70.08
GP73	0.649	4.937	< 0.001	229.22 ng/ml	40.98	81.04	68.54
AFP + IL-6	0.873	19.537	< 0.001	—	81.97	75.09	77.23
AFP + IL-6 + GP73	0.881	20.490	< 0.001	—	75.41	85.13	82.10

注：^a：与 ROC = 0.5 相比较；“—”：无相关数据

表4 AFP、GP73 和 IL-6 对失代偿期 HLC 与 PHC 的鉴别诊断

标志物	AUC	Z值	^a P值	临界值	敏感性 (%)	特异性 (%)	准确性 (%)
AFP	0.797	9.913	< 0.001	29.44 ng/ml	64.75	88.54	75.22
IL-6	0.568	1.721	0.085	21.80 pg/ml	56.56	64.58	60.09
GP73	0.505	0.139	0.889	146.62 ng/ml	40.16	67.71	52.29

注：^a：与 ROC = 0.5 相比较

正相关,也与慢性HBV感染者肝脏炎症损伤包括由HLC引起的肝功能损伤关系密切。且GP73的表达受炎症因子调控,在培养的肝细胞中,IFN- γ 、IL-6能上调胞内GP73水平, TNF- α 能下调胞内GP73表达^[21-22]。因此, IL-6和GP73可能反映了肝脏炎症损伤状态,乙型肝炎患者体内高水平的IL-6和GP73应获得治疗者的足够重视。

肝细胞癌是世界范围内最常见、最具侵袭性的恶性肿瘤之一,多数肝癌患者诊断时已发展至中晚期,疗效差^[23-24]。肝硬化是肝细胞癌最重要的危险因素,肝癌多是在乙型肝炎后肝硬化的基础上发展而来^[25]。现有的PHC筛查指标如AFP、影像学检查等无法监测到早期PHC的发生,故筛查早期肝癌或是从肝硬化中鉴别诊断出肝癌的高危人群是目前急需解决又最棘手的目标。IL-6被认为是与癌症相关的炎症因子之一,介导的STAT3磷酸化所调控的基因与肝细胞癌、肺癌、结肠癌、乳腺癌、前列腺癌、卵巢癌及血液系统肿瘤的发生密切相关^[26-31]。本研究中PHC组患者血清IL-6水平异常升高,IL-6对肝癌诊断的高敏感性可做为肝癌经典预测因子AFP的补充,弥补AFP筛选肝癌时敏感性低,常发生漏检的问题。但由于血清IL-6并非在肝癌中特异性升高,肝硬化尤其是失代偿期肝硬化的血清IL-6水平也较高,导致血清IL-6诊断肝癌的特异性和准确性不理想,亦无法从失代偿期肝硬化中区分肝癌。尽管血清IL-6在肝癌的诊断价值上尚有不足之处,但其高敏感性仍然能帮助治疗人员注意到高水平血清IL-6患者中患有恶性肝脏肿瘤的可能性。GP73是最近作为一种有潜力的诊断早期肝癌的标志物而受到广泛研究的高尔基体II型跨膜蛋白^[32-34],但如前所述,由于其并非在肝癌中特异性升高,其对肝癌的诊断价值受到越来越多的质疑。本研究中GP73诊断肝癌的曲线下面积、敏感性都不高,也无法区分失代偿期肝硬化和肝癌。因此,GP73不适合做为诊断肝癌的分子标志物,但可作为反映慢性HBV感染者疾病进展和病情严重程度的分子指标。

参 考 文 献

- [1] Songle H, Binh VQ, Duy DN, et al. Serum cytokine profiles associated with clinical presentation in vietnamese infected with hepatitis B virus[J]. J Clin Virol,2003,28(1):93-103.
- [2] Zhang F, Yao S, Zhang M, et al. Roles of circulating soluble interleukin (IL)-6 receptor and IL-6 receptor expression on CD4⁺ T cells in patients with chronic hepatitis B[J]. Int J Infect Dis,2011,15(4):e267-e271.
- [3] Tang S, Liu Z, Zhang Y, et al. Rather than rs1800796 polymorphism, expression of interleukin-6 is associated with disease progression of chronic HBV infection in a chinese han population[J]. Dis Markers,2013,35(6):799-805.
- [4] Prieto J. Inflammation, HCC and sex: IL-6 in the centre of the triangle[J]. J Hepatol,2008,48(2):380-381.
- [5] Riener MO, Stenner F, Liewen H, et al. Golgi phosphoprotein 2 expression in liver tumours and its value as a serum marker in hepatocellular carcinomas[J]. Hepatology,2009,49(5):1602-1609.
- [6] 许正锯,潘兴南,魏开鹏,等.血清高尔基体蛋白73与慢性乙型肝炎病毒感染者肝脏炎症损伤的相关性[J/CD]. 中华实验和临床感染病杂志(电子版),2014,8(5):598-604.
- [7] Xu Z, Liu L, Pan X, et al. Serum Golgi protein 73 (GP73) is a diagnostic and prognostic marker of chronic HBV liver disease[J]. Medicine (Baltimore),2015,94(12):e659.
- [8] Block TM, Comunale MA, Lowman M, et al. Use of targeted glycoproteomics to identify serum glycoproteins that correlate with liver cancer in woodchucks and humans[J]. Proc Natl Acad Sci,2005,102(3):779-784.
- [9] 中华人民共和国卫生部.原发性肝癌诊疗规范(2011年版)[J]. 临床肿瘤学杂志,2011,16(10):929-946.
- [10] 中华医学会肝病学会,中华医学会感染病分会.慢性乙型肝炎防治指南(2015年版)[J/CD]. 中华实验和临床感染病杂志(电子版),2015,9(5):1-19.
- [11] Bruix J, Sherman M. Management of hepatocellular carcinoma: an update[J]. Hepatology,2011,53(3):1020-1022.
- [12] 马斌荣主编. SPSS在医学统计中的应用[M]. 4版. 北京: 科学出版社,2010:202-228.
- [13] Zhou YH, Wu C, Zhuang H. Vaccination against hepatitis B: the Chinese experience[J]. Chin Med J (Engl),2009,122(1):98-102.
- [14] Chu CJ, Lok AS. Clinical significance of hepatitis B virus genotypes. Hepatology,2002,35(5):1274-1276.
- [15] Thursz M. Genetic susceptibility in chronic viral hepatitis[J]. Antiviral Res,2001,52(2):113-116.
- [16] Luo MX, Wong SH, Chan MT, et al. Autophagy mediates hbx-induced nuclear factor-kappaB activation and release of IL-6, IL-8, and CXCL2 in hepatocytes[J]. J Cell Physiol,2015,230(10):2382-2389.
- [17] Naugler WE, Sakurai T, Kim S, et al. Gender disparity in liver cancer due to sex differences in MyD88-dependent IL-6 production[J]. Science,2007,317(5834):121-124.
- [18] Naugler WE, Karin M. The wolf in sheep's clothing: the role of interleukin-6 in immunity, inflammation and cancer[J]. Trends Mol Med,2008,14(3):109-119.
- [19] Caixia X, Yanning L, Zhi C. Involvement of interleukin 6 in hepatitis B viral infection[J]. Cell Physiol Biochem,2015,37(2):677-686.
- [20] Kladney RD, Cui X, Bulla GA, et al. Expression of GP73, a resident Golgi membrane protein, in viral and nonviral liver disease[J]. Hepatology,2002,35(6):1431-1440.
- [21] Liang H, Block TM, Wang M, et al. Interleukin-6 and oncostatin M are

- elevated in liver disease in conjunction with candidate hepatocellular carcinoma biomarker GP73[J]. *Cancer Biomark*,2012,11(4):161-171.
- [22] Wang F, Long Q, Gong Y, et al. Epithelium-Specific ETS (ESE)-1 upregulated GP73 expression in hepatocellular carcinoma cells[J]. *Cell Biosci*,2014,4(1):76.
- [23] Block TM, Mehta AS, Fimmel CJ, et al. Molecular viral oncology of hepatocellular carcinoma[J]. *Oncogene*,2003,22(33):5093-5107.
- [24] Sherman M. Hepatocellular carcinoma: epidemiology, surveillance and diagnosis[J]. *Sem Liver Dis*,2010,30(1):3-16.
- [25] Calvarusa V, Graxi A. Regression of fibrosis after HBV antiviral therapy, Is cirrhosis reversible?[J]. *Liver Int*,2014,34 (Suppl 1):85-90.
- [26] Dienz O, Rincon M. The effects of IL-6 on CD4⁺ T cell responses[J]. *Clin Immunol*,2009,130(1):27-33.
- [27] Grivennikov S, Karin M. Autocrine IL-6 signaling: a key event in tumorigenesis?[J]. *Cancer Cell*,2008,13(1):7-9.
- [28] Bromberg J, Wang TC. Inflammation and cancer: IL-6 and STAT3 complete the link[J]. *Cancer Cell*,2009,15(2):79-80.
- [29] Kruoda K, Nakashima J, Kanao K, et al. Interleukin 6 is associated with cachexia in patients with prostate cancer[J]. *Urology*,2007,69(1):113-117.
- [30] Berasain C, Castillo J, Perugorria MJ, et al. Inflammation and liver cancer: New molecular links[J]. *Ann N Y Acad Sci*,2009,1155:206-221.
- [31] Chang TS, Wu YC, Chi CC, et al. Activation of IL-6/igf1R confers poor prognosis of hbv-related hepatocellular carcinoma through induction of oct4/nanog expression[J]. *Clin Cancer Res*,2015,21(1):201-210.
- [32] Mao Y, Yang H, Xu H, et al. Golgi protein 73 (GOLPH2) is a valuable serum marker for hepatocellular carcinoma[J]. *Gut*,2010,59(12):1687-1693.
- [33] Marrero JA, Romano PR, Nikolaeva O, et al. GP73, a resident Golgi glycoprotein, is a novel serum marker for hepatocellular carcinoma[J]. *J Hepatol*,2005,43(6):1007-1012.
- [34] Sum YL, Yang HY, Mao YL, et al. Increased Golgi protein 73 expressed in hepatocellular carcinoma tissue correlates with tumor aggression but not survival[J]. *J Gastroenterol Hepatol*,2011,26(7):1207-1212.

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