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基础研究 BASIC RESEARCH

STAT3在肝衰竭组织中的表达及其与肝前体细胞增殖的关系

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■背景资料
肝衰竭组织中存在肝前体细胞的活化及增殖, 由于肝前体细胞具有双向分化潜能, 他可以分化为肝细胞及胆管细胞, 故肝前体细胞可望成为严重肝病细胞替代疗法以及人工肝的供体细胞, 因此使其成为当前的一个研究热点, 尤其肝前体细胞活化增殖及分化机制的研究成为探讨的焦点.

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Expression of STAT3 in liver failure tissue and the relationship between expression of STAT3 and the proliferating features of hepatic progenitor cells

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Abstract

AIM: To investigate the proliferating features of hepatic progenitor cells (HPCs) and the expression of p-STAT3 in liver failure.

METHODS: Liver tissues taken from 76 patients with liver failure and acute or chronic light hepatitis were tested for the expression of HPCs with OV6 by immunohistochemistry. Meanwhile, expression of cytokeratin 19 (CK19) and p-STAT3 was also detected in liver tissues by immunohistochemistry.

RESULTS: There were a lot of proliferating ductars in subacute and acute-on-chronic liver failure by immunohistochemical staining with CK19. The percentage of patients with liver failure positive for CK19 (62.5%) was significantly higher than that in common hepatitis (30%) ($P < 0.05$). The percentage of cases of liver failure positive for OV6 (85.7%) was significantly higher than that in common hepatitis (35.0%) ($P < 0.05$). The percentage of patients with liver failure positive for p-STAT3 (67.9%) was significantly higher than that in common hepatitis (25%) ($P < 0.05$), the expression of OV6 had a positive correlation with that of CK19 ($r_s = 0.689$)and p-STAT3 ($r_s = 0.239$).

CONCLUSION: HPCs are frequently detected in patients with liver failure. Expression of p-STAT3 is significantly higher than that in common hepatitis and is associated with the proliferation of HPCs. Thus, p-STAT3 might participate in the proliferation of HPCs.

Key Words: Liver failure; p-STAT3; Immunohistochemistry

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摘要

目的: 探讨p-STAT3在肝衰竭组织中的表达及其与肝前体细胞(HPC)增殖的关系.

方法: 对76例肝衰竭组织及急慢性轻型肝炎组织进行HE染色以观察病变特点; 应用免疫组织化学的方法对肝衰竭组织及急慢性轻型肝炎组织进行OV6, CK19及p-STAT3检测.

结果: CK19免疫组化结果表明, 亚急性肝衰竭(SALF)组织及慢加急性(亚急性)肝衰竭

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(ACLF)组织中可见大量增生的胆管, 包括典型增生胆管和非典型增生胆管. 肝衰竭组织的CK19阳性率(62.5%)明显高于急慢性轻型肝炎的阳性率(30%)(P<0.05). 肝衰竭组织的OV6阳性率(85.7%)明显高于急慢性轻型肝炎的阳性率(35.0%)(P<0.05). p-STAT3的阳性表达主要位于汇管区增生的胆管细胞、肝前体细胞、炎性细胞、窦内皮细胞及肝细胞的胞核. 肝衰竭组织的p-STAT3阳性率(67.9%)明显高于急慢性轻型肝炎的阳性率(25%)(P<0.05). 相关分析表明, OV6的表达与CK19及p-STAT3表达成正相关(r_s = 0.689, r_s = 0.239, P<0.05).

结论: 肝衰竭组织中存在HPC的增殖; 肝衰竭组织中p-STAT3的表达增加, 与HPC表达成正相关, 提示p-STAT3参与肝衰竭组织中HPC的增殖调控.

关键词: 肝衰竭; 免疫组织化学; 磷酸化STAT3

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0 引言

各种病因(包括病毒性、化学性及酒精性)引起的肝衰竭严重威胁人类健康. 迄今国际上对肝衰竭的定义、分类和诊断尚无一致意见. 2006-09我国制订了第一部《肝衰竭诊疗指南》[1-2], 将肝衰竭分为急性肝衰竭(acute liver failure, ALF)、亚急性肝衰竭(subacute liver failure, SALF)、慢加急性(亚急性)肝衰竭(acute-on-chronic liver failure, ACLF)及慢性肝衰竭(chronic liver failure, CLF).

肝脏具有较强的再生能力, 当肝损伤较轻时, 通常由残存的肝细胞再生以代偿肝功能. 但当严重肝损伤或其他原因影响了正常肝细胞的复制增殖能力时, 可以有肝干细胞的活化、增殖和分化. 在动物实验中为肝卵圆细胞, 在人类中为管状细胞或小肝细胞样细胞[3-8], 称之为肝前体细胞(hepatic progenitor cell, HPC). 目前研究表明肝衰竭组织中存在HPC的活化及增殖, 他可以分化为肝细胞及胆管细胞. 如果能诱导HPC的活化, 增殖与分化则为干细胞移植带来富足的细胞来源. 但HPC的活化、增殖及分化机制尚不清楚.

信号转导子和转录激活子家族(signal transducer and activator of transcription, STATs)是一种存在于细胞质与酪氨酸磷酸化信号通道偶联的双功能蛋白. STAT3参与了许多细胞因子及生长因子介导的细胞增殖及分化过程[9-16].

本文旨在研究急、慢性肝衰竭组织中HPC的增殖情况及STAT3的表达.

■研发前沿

信号转导子和转录激活子家族STATs是一种存在于细胞质与酪氨酸磷酸化信号通道偶联的双功能蛋白. STAT3参与了许多细胞因子及生长因子介导的细胞增殖及分化过程, 但其在肝前体细胞增殖及分化过程中的作用有待进一步研究.

1 材料和方法

1.1 材料 1965-2005年中国医科大学第一临床学院尸检病例、肝脏外科手术病例(包括肝移植)及肝活检病例共76例. 病理诊断符合2006年《肝衰竭诊疗指南》诊断标准[2]. 年龄6-68岁, 男性55例, 女性21例. 其中ALF20例、SALF10例、ACLF8例及CLF18例. 另外选取轻度急性病毒性肝炎(acute viral hepatitis, AH)及轻度慢性病毒性肝炎(chronic viral hepatitis, CH)20例作为对照. 所有病例肝组织标本均经40 g/L甲醛固定,石蜡包埋, 4 μm厚连续切片. 小鼠抗人OV6 mAb由美国BROWN大学Hixson教授惠赠. 兔抗人Phospho-STAT3(Tyr705)多克隆抗体购自Cell Signaling公司; 小鼠抗人细胞角蛋白19(Cytokeratin19, CK19)mAb购自Neo Markers公司. SP免疫组化试剂盒及DAB酶底物显色试剂盒购自福州迈新生物技术公司.

1.2 方法

1.2.1 肝组织学检查: 石蜡切片进行HE染色, 观察肝脏组织学基本病理改变.

1.2.2 免疫组织化学染色: 连续石蜡切片经脱蜡后, 以高温高压进行抗原修复. 滴加A液(SP试剂盒中, 即30 mL/L过氧化氢溶液)37℃ 30 min, 以灭活内源性过氧化物酶. PBS洗3次; 滴加B液(SP试剂盒中, 即正常山羊血清)封闭37℃ 30 min; 吸去血清, 滴加一抗(p-STAT3稀释倍数1∶100, CK19稀释倍数1∶100; OV6稀释倍数1∶200)4℃湿盒内孵育过夜. 以不加一抗的PBS作为阴性对照. PBS洗3次; 滴加C液(SP试剂盒中, 即二抗), 37℃湿盒内孵育30 min; PBS洗3次; 滴加D液(SP试剂盒中, 即SP复合物), 37℃湿盒内孵育30 min; PBS洗3次; DAB显色, 苏木素复染, 中性树胶封片.

1.2.3 免疫组化结果判定: (1)OV6免疫组化半定量[12]: OV6表达于细胞质, 呈现棕色颗粒为阳性. 每张切片随机选取5个高倍视野, 每个视野计数100个细胞, 计算阳性细胞的百分数. OV6染色阳性细胞为HPC. "-": 无HPC或有少量HPC; "+": 灶性HPC; "++": 连续性HPC, 但范围

■相关报道
有研究表明在人类重型肝炎肝组织中存在着肝前体细胞的增殖, 并且肝前体细胞的数目与肝病的严重程度密切相关. 另有研究证实STAT3参与肝损伤后肝细胞再生的调控, 促进受损肝脏肝细胞的增殖, 但其在肝衰竭组织中肝前体细胞增殖中的作用尚不清楚.

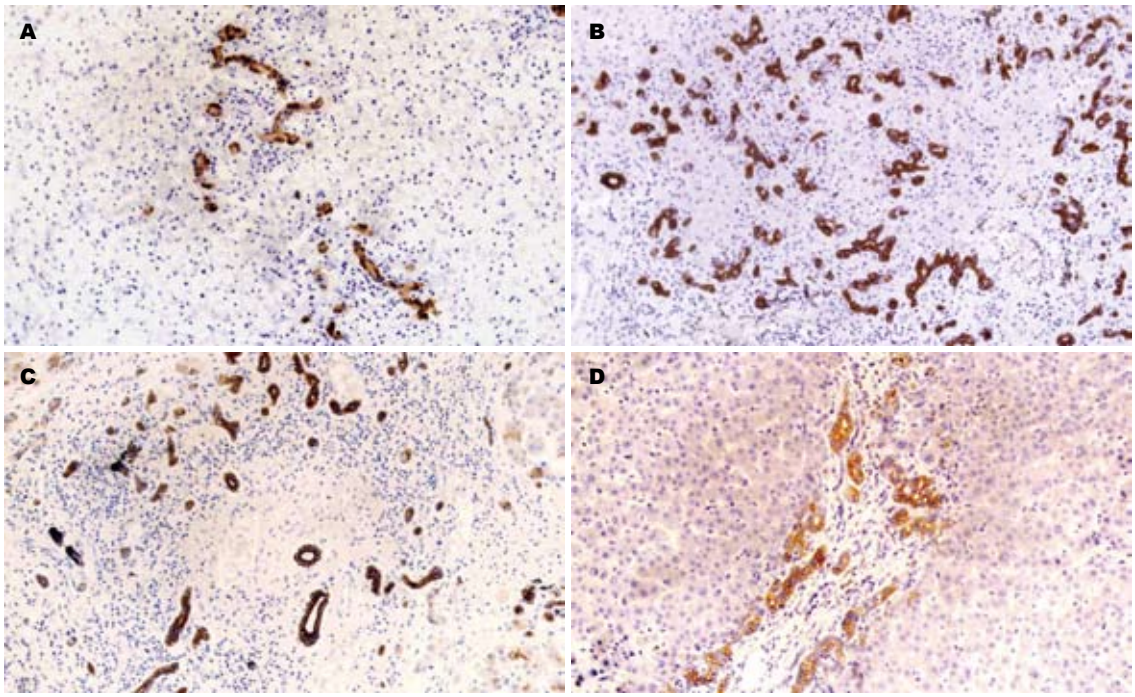

图 1 CK19在各型肝衰竭组织中的表达(免疫组化SP法 × 200). A: ALF; B: SALF; C: ACLF; D: CLF.

<50%汇管区和纤维间隔; “+++”: 连续性HPC, 但范围>50%汇管区和纤维间隔. 以“-”为阴性; “+”“++”及“+++”为阳性. (2)CK19及p-STAT3免疫组化染色结果判定[17]: 每张切片随机选取5个高倍视野, 每个视野计数100个细胞, 计算阳性细胞的百分数. CK19表达于细胞质, p-STAT3表达于细胞核, 呈现棕色颗粒为阳性. 无着色或阳性表达率≤25%为阴性; >25%为阳性.

统计学处理 所有资料采用SPSS13.0统计软件进行分析. 不同组比较采用χ^2检验, 相关分析采用Spearman法. P<0.05为差异有统计学意义.

2 结果

2.1 肝衰竭肝组织病理特征 各型肝衰竭组织HE染色结果如下: (1)ALF: 肝细胞大块或亚大块性坏死, 坏死面积≥肝实质的2/3, 残留的肝细胞多集中于汇管区周围. (2)SALF: 可见亚大块坏死或桥接坏死, 坏死区周围出现大量增生的小胆管及胆管样肝细胞团, 往往沿塌陷网状支架呈无序的再生, 残留的肝细胞有增生. (3)ACLF: 在慢性肝病背景上发生新的程度不等的大块、亚大块性肝细胞坏死或桥接坏死. 出现大量增生的小胆管及胆管样肝细胞团. (4)CLF: 弥漫性肝脏纤维化及假小叶形成, 伴有局灶性肝细胞坏死.

2.2 CK19免疫组化染色结果 ALF肝组织中可见汇管区有CK19染色阳性的胆管, 胆管多含有管腔, 少数为不含管腔的非典型增生的假胆管. SALF及ACLF肝组织中可见大量增生的胆管, CLF肝组织中也可见到一些增生的胆管. 从增生的胆管结构而言, 可观察到两种类型的增生胆管, 即典型增生胆管和非典型增生胆管. 典型增生胆管可见到管腔结构及清晰的边界; 而非典型增生胆管无明确的管腔结构, 而且周围边界模糊(图1). 肝衰竭组织CK19阳性率(62.5%)明显高于急、慢性轻型肝炎组织的阳性率(30%)(P<0.05, 表1).

表 1 OV6, CK19, p-STAT3在肝衰竭组织中的表达

	OV6		CK19		p-STAT3	
	−	+	−	+	−	+
急慢性轻型肝炎	13	7	14	6	15	5
肝衰竭	8	48	21	35	18	38
χ^2	18.95		6.256		11.018	
P	<0.0005		0.012		0.001	

2.3 OV6免疫组化染色结果 OV6是肝前体细胞的标记抗体, 阳性染色呈现胞质棕色表达. OV6染色阳性的细胞主要有两种形式. 大部分是组成非典型增生胆管的管状细胞. 细胞体积较小, 有卵圆形的核, 核体积较大, 细胞胞质较少, 位于纤维间隔或炎症灶周围, 以闭合的实心条索或细胞团的形式存在. 另一种是汇管区出现的小肝细胞样细胞(图2).

急、慢性轻型肝炎仅见极少量的OV6阳性

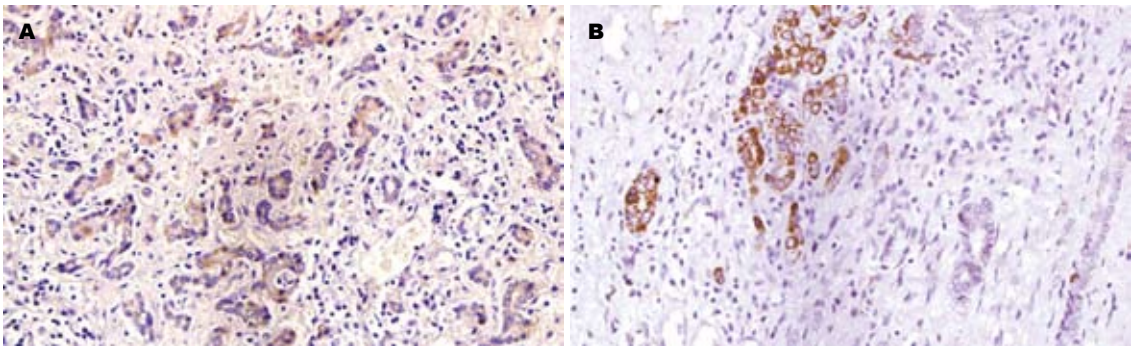

图 2 OV6在肝衰竭组织中的表达(免疫组化SP法 × 400). A: SALF, 非典型增生胆管表达阳性; B: ACLF, 小肝样细胞表达阳性.

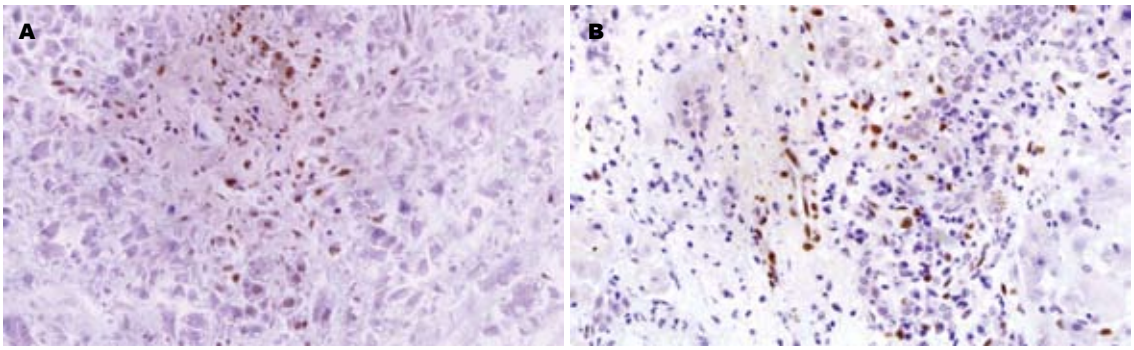

图 3 p–STAT3在肝衰竭组织中的表达(免疫组化SP法 × 400). A: ALF; B: SALF.

细胞, ALF组织阳性细胞也较少. 在SLF及ACLF组织中表达增加, 其中以ACLF组织表达最多. CLF肝组织中OV6阳性的细胞数有所减少. 统计学分析表明肝衰竭组织的OV6阳性率(85.7%)明显高于急、慢性轻型肝炎组织的阳性率(35.0%)(P<0.05). 相关分析表明, OV6的表达与CK19的表达成正相关(r_s = 0.689, P<0.05, 表1).

2.4 p-STAT3免疫组化染色结果 急、慢性轻型肝炎仅见少量的p-STAT3表达, 阳性表达的p-STAT3主要位于汇管区炎性细胞的胞核呈棕色颗粒. ALF, SLF, ACLF及CLF肝组织中p-STAT3的表达增加, 主要位于汇管区增生的胆管细胞、肝前体细胞、炎性细胞、窦内皮细胞及肝细胞的胞核(图3). 肝衰竭组织的p-STAT3阳性率(67.9%)明显高于急、慢性轻型肝炎组织的阳性率(25%)(P<0.05). 相关分析表明, p-STAT3的表达与OV6的表达呈正相关(r_s = 0.239, P<0.05, 表1).

3 讨论

1992年De Vos *et al*[18]在慢性肝病患者的肝脏组织中检测到一种类似大鼠肝卵圆细胞的细胞, 并研究了超微结构. 研究发现HOC具有独特的细胞形态, 细胞体积较小, 约为正常肝细胞的1/4至1/2大小, 整个细胞大部分为卵圆形胞核所占据, 表现为原始幼稚未分化细胞的超微结构特点. 他同时兼备肝细胞和胆管上皮细胞的特点. 有研究证实在人类重型肝炎肝组织中也存在着这种细胞[19-30], 称为HPC.

本实验研究了各型肝衰竭患者肝组织中HPC的增生情况. 结果表明ALF组织中仅有很少量的OV6阳性的HPC的存在, 而SALF及CALF组织中可见到大量的OV6表达阳性的HPC细胞. CLF肝组织中OV6阳性的细胞数有所减少.

Lowes *et al*[31]研究了HPC数目与遗传性血色病、慢性酒精性肝病、慢性肝炎和肝硬化等慢性肝病的关系, 发现HPC数目与肝病的严重程度密切相关. 病情越重, HPC数目就越多, 增生就越活跃.

HPC活化、增殖及分化的机制目前尚不清楚. STAT3是在1994年作为白细胞介素-6(interleukin, IL-6)信号传递中的急性期反应因子被纯化的. STAT3广泛表达于不同类型的细胞和组织中, 可被IL-6家族、表皮生长因子(epithelial growth factor, EGF)、肝细胞生长因子(hepatic growth factor, HGF)和磺胺噻唑激活, 发生

■创新盘点

本文应用免疫组织化学的方法研究了不同肝衰竭组织中肝前体细胞的活化及增殖情况, 表明肝衰竭组织中存在着肝前体细胞的增殖, 并发现肝衰竭组织中STAT3表达增加, 证实STAT3可能参与了肝前体细胞的活化与增殖.

■应用要点
通过本课题的研究, 可了解肝前体细胞增殖、分化的某些调控因素, 阐明信号转导分子在肝前体细胞增殖分化中的调控作用, 为肝前体细胞的基础研究和临床应用研究提供试验依据.

磷酸化, 磷酸化的STAT3可以通过调控核因子-kb等转录因子进而参与细胞的增殖及分化[32-41].

Sakuda *et al*[42]研究发现STAT3在正常的肝脏中以未活化的形式存在. 在大鼠肝脏切除2/3不损伤留下的肝叶的情况下, 活化的STAT3在30 min内出现, 在3 h达到高峰, 提示STAT3具有促进肝脏再生的作用. 参与肝细胞再生过程的STAT3的活化主要由IL-6介导, IL-6基因缺陷小鼠的STAT3活化水平降低, 肝细胞再生时DNA合成受抑制[43-47]. 上述研究提示STAT3参与肝损伤后的肝细胞再生的调控[48-52]. 但STAT3在急、慢性肝衰竭组织中的表达及其对HPC增殖的调控尚不清楚.

本实验研究表明ALF肝组织可见少量的p-STAT3表达, 主要位于汇管区的炎性细胞.而SLF及ACLF肝组织中p-STAT3的表达增加, 除了汇管区的炎性细胞外, 增生的胆管细胞、肝前体细胞、窦内皮细胞及再生肝细胞的胞核均出现阳性表达.

Sanchez *et al*[35]应用二乙酰氨基芴结合部分肝切除(AAF/PH)建立HPC增殖的动物模型, 证实了STAT3的表达增加促进HPC的增殖, 并且认为活化的STAT3具有调控HPC分化的作用. 因此我们推测STAT3在急、慢性肝损伤过程中可以促进肝细胞及HPC的增殖以修复受损肝脏.

总之, 本研究表明, 在SALF, ACLF及CLF肝组织中存在着HPC的活化及增殖, STAT3的表达促进HPC的增殖.

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■同行评价
本文研究内容新颖, 具有一定的创新性, 对临床具有一定的参考价值.

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