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文献综述 REVIEW

肝再生终止阶段的研究进展

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Progress in research of the termination of liver regeneration

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Abstract

The liver is the body's most important detoxification organ and has an extreme ability to regenerate. The regeneration process can be divided into three stages: initiation, proliferation and termination. Most of previous studies focus on the initial stage and proliferative stage, while the mechanism for the proper termination of liver regeneration is still poorly understood. The termination stage involves a variety of cytokines and growth factors, which mainly function to inhibit mitogen-mediated liver cell growth-promoting effect and promote the apoptosis of excessively proliferating liver cells. In this review we will discuss the major factors involved in the termination of liver regeneration.

Key Words: Liver regeneration; Termination; Transforming growth factor β1; Hippo kinase pathway; Integrin-linked kinase; Glypican; Activin; Interleukin-1

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摘要

肝脏作为体内最重要的解毒器官, 具有极强的再生能力. 肝再生研究一直是再生医学研究领域的热点, 其再生过程可分为起始阶段、增殖阶段以及终止阶段. 目前研究大都集中在肝再生的起始以及增殖阶段, 对于使肝再生恰当终止的机制研究仍知之甚少. 肝再生终止阶段涉及多种细胞因子与生长因子, 其功能主要体现在2方面: (1)抑制有丝分裂原对于肝细胞增长的促进作用; (2)通过某种途径促进过多增殖的肝细胞凋亡. 本文针对目前肝再生的终止阶段研究所涉及的主要的因子综述如下.

关键词: 肝再生; 终止; 转换生长因子β1; Hippo通路; 整合素连接激酶; 磷脂酰肌醇; 激活素; 白介素1

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0 引言

肝再生是指因各种因素如中毒、感染、肝移植等导致的肝脏部分性损伤而引起的肝修复过程. 肝损伤后处于静息期的肝细胞通过内在的免疫系统产生的一些细胞因子如IL-6、TNF-α等以及其受体的作用启动了肝再生进程. 而此后肝细胞在一些有丝分裂原诸如肝细胞生长因子(hepatocyte growth factor, HGF)与表皮生长因子(epidermal growth factor, EGF)的刺激下, 迅速进入了增殖阶段, 当其增殖乏力时即进入肝再生终止阶段. 在肝再生末期, 肝重相对精确地被调整以与原肝重相适应[1]; 同时, 通过TUNEL标记分析发现在小鼠肝再生的末期会出现一小部分肝细胞凋亡[2], 这似乎证

■背景资料
肝再生主要分为3个阶段, 起始阶段即静止的肝细胞重新进入细胞周期; 增殖阶段主要指肝细胞在促有丝分裂原如HGF, TGFβ和EGF刺激下进入细胞周期的G_1期; 当细胞增殖事件完成后, 肝脏的组织学结构重新排列和恢复, 肝再生便进入终止阶段.

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■研发前沿
目前关于肝再生终止阶段的研究已逐渐从TGFβ、ILK等单一细胞因子方面的研究逐步向TGFβ与activin, ILK与细胞外基质等多因子交互作用方面转移, 同时Hippo通路、小干扰RNA正日益成为研究热点.

明存在某种机制以对肝细胞数量不恰当增长时进行纠正. 相比于肝再生起始及增殖阶段的研究, 肝再生终止阶段的具体机制十分复杂且尚不清楚. 通过再生肝细胞的体外培养以及对特异性敲除或过表达相关基因的动物模型的研究, 发现肝再生终止阶段可能与转换生长因子β1(transforming growth factor β, TGF-β1)、Hippo通路、激活素A(activin A)、整合素连接激酶(integrin-linked kinase, ILK)、磷脂酰肌醇3(glypican-3)、白介素1(interleukin-1, IL-1)等因子有关. 而本文通过在CNKI、维普、万方等国内文献数据库中检索发现, 国内目前并没有单独关于肝再生终止阶段的相关综述, 但是研究肝再生的终止不仅对于肝病诸如肝癌、肝纤维化等的治疗具有重要的临床价值, 而且对于研究细胞可控增殖以及解决肝脏移植方面都有重要意义.

1 TGF-β1

TGF-β1, 其超家族成员还包括一些其他细胞因子及多肽, 如激活素、抑制素(inhibin)及骨形态发生蛋白(bone morphogenetic protein, BMP)[3]. 在哺乳动物体内存在3种TGF-β(TGF-β1, 2, 3), 而TGF-β2, 3在肝再生过程中的功能尚不明确[4]. TGF-β有3种受体(TGF-βRⅠ-Ⅲ), 通过其Ⅰ型和Ⅱ型受体复合物激活下游蛋白, TGF-β1Ⅲ型受体并不直接参与信号传递, 主要调节TGF-β与信号受体的结合, 进而调控细胞的生长和死亡, 其受体复合物是由3种相互作用的膜蛋白(TGFβR1-3)装配而成[3,5,6].

TGF-β1主要由肝非实质性细胞如肝星状细胞产生, 但也有研究表明其可从肝细胞及血小板中产生[7]. 对小鼠进行肝部分切除术(partial hepatectomy, PH)后, TGFβ1 mRNA一般于4 h后表达量开始升高, 术后72 h左右时达到峰值[8], 而肝细胞膜表面的TGF-βⅠ-Ⅲ型受体的mRNA与蛋白表达量则会立即降低并于24 h达到最低点, 此时正是肝细胞DNA合成的高峰, 其中Ⅱ型受体于术后120 h(肝细胞DNA合成已基本完成)恢复到术前水平, Ⅰ、Ⅲ型受体也回复到术前水平的60%[9]. 而TGF-β1蛋白表达量则在肝切后2-6 h快速升高, 但在肝细胞增殖期间会暂时降低[10,11]. Macias-Silva等[12]认为这可能是由于TGF-β1受体减少或抑制TGF-β1的因子如SnoNs、Ski引起. Leu等[10]则认为是由于胰岛素样生长因子结合蛋白(insulin-like growth factor binding protein, IGFBP)减少引起. 另外, 有研究表明对未进行肝切的小鼠注射TGF-β1受体抑制剂能够增强肝细胞的增殖[13]. 这说明TGF-β1能够中和HGF的促有丝分裂作用[14,15]. TGF-β1与HGF在正常肝组织中分别结合肝细胞外基质(extracellular matrix, ECM)中的核心蛋白与葡萄糖胺聚糖[16]. 肝切后, 肝细胞外基质的重排使得尿激酶活性增强催化纤溶蛋白酶原转化为纤溶蛋白酶, 进而促使TGF-β1与HGF获得活性进入血浆, 但具有活性的TGF-β1能迅速被血浆中的α2巨球蛋白所结合灭活; 在肝再生后期, 随着大量肝细胞出现并在细胞膜上表达了大量TGF-β1受体时, 再生肝细胞对TGF-β1的高分子无活性形式进行分解, 从而发挥其抑制肝细胞增殖的作用[3,16,17]. 同时, TGF-β1会对尿激酶产生抑制作用, 而且也会刺激间充质细胞产生新的细胞外基质结合HGF, 从而也对肝再生的进程进行抑制[3,18].

在分子水平上, TGF-βRⅠ通过结合其细胞膜表面的Ⅱ型受体并激活其磷酸化激酶活性, TGF-βRⅠ能够识别此复合物并与之结合, 后又被TGF-βRⅡ磷酸化激酶磷酸化激活, 从而激活了Smad2/3羧基末端的SSXS序列, 后者再与Smad4结合形成异源寡聚体. Smad2/3-Smad4复合物进入细胞核后通过直接与DNA结合或与其他转录因子形成稳定复合物对目的基因进行激活调控[6,19,20]. 至于TGF-β1受体表达量回升的原因, Michalopoulos等[3]认为这可能是由新形成的窦状毛细血管内的氧分压增高刺激了肝细胞表达所致. 根据Russell等[21]的研究表明, 在肝再生不同时间点对小鼠静脉注射TGF-β1能够抑制肝细胞的增殖, 但此效果是暂时性的, TGF-β1并不会即刻终止肝再生进程. 而就TGF-β的激活, 有研究者认为是非阳离子依赖性的甘露糖六磷酸受体(cation-independent mannose 6-phosphate receptor, CIMPR)的作用. CIMPR会在肝再生时过表达, 其基因在G_1期表达, 介导了潜在的前TGF-β激活, 从而在肝再生终止期激活TGF-β进而对肝细胞产生作用[22]. 而为了检验内源性TGF-β1在肝再生中的作用, Romero-Gallo等[23]利用肝细胞被特异性敲除TGF-β1Ⅱ型受体的小鼠进行肝再生实验, 研究发现肝切后, 肝细胞增殖期加速7 d, 肝重体质量比也呈上升趋势, 但此作用效果也是暂时性的.

就TGF-β与细胞周期蛋白之间的关系, 有研

究表明在TGF-βⅡ型受体特异性敲除的小鼠中P130蛋白的磷酸化程度升高, 且cyclin E的表达量以及肝重也有所升高. Breitkopf等[24]进行相似研究, 发现TGF-β能使cyclin E/cdk2复合体失活, 导致cdk2和cdk4转录活性下降, 进而抑制肝细胞增殖, 即TGF-β主要调控肝细胞在G_1期→S期的转变, 使肝细胞停滞在G_1期. 值得注意的是, 过表达TGF-β1的转基因小鼠有正常的肝再生, 但是会增强其肝细胞纤维化的程度[25], 并引起肾小球肾炎[26]. Oe等[27]发现, 除非同时灭活activin受体, 否则特异性敲除TGF-β受体基因的小鼠肝再生过程表现为基本正常, 进一步的研究也显示activin A及其2型受体也可以使Smad激活. 由此得出结论, TGF-β1并不是唯一调节肝再生终止过程的细胞因子. 此外, 也有研究表明TGF-β1能通过不依赖c-Jun的机制诱导肝细胞凋亡[28-30].

2 Hippo通路

已有大量研究表明Hippo通路在控制器官大小及再生方面的重要作用. Hippo通路最初被认为主要通过抑制细胞增殖及促进凋亡来限制器官大小, 但目前也有研究发现其在调节干细胞及祖细胞的自我更新及扩张方面的作用[31-33]. Hippo通路的激活主要由细胞极性、细胞黏附以及细胞连接蛋白所调控[31], 而在哺乳动物细胞内Hippo通路的激活则部分由细胞接触所致[34].

Hippo通路分子主要包括有Mst1/2, sav1, Lats1/2, Mob1, YAP及其同源蛋白TAZ. 作为Hippo通路的核心组件Mst1/2是一种前凋亡因子, 当细胞处于凋亡压力时, 由半胱天冬酶(caspase)剪切激活[35]. sav1则通过SARAH区与Mst1/2相互作用[36], 其具体功能与Mst1/2的核转运有关[37]. Lats1/2是Mst1/2的直接底物, 可被其磷酸化所激活[38]. Mob1可与Lats1/2形成复合物, 也能被Mst1/2磷酸化激活, 这也导致其与Lats1/2之间相互作用的加强[39]. 最后处于活性状态的Lats1/2再通过磷酸化抑制转录辅因子YAP/TAZ的活性, 从而对器官大小及组织再生进行调控[34,40]. 有趣的是, 由Lats磷酸化的YAP能够诱导其自身降解[41], 这对抑制细胞过度增殖有重要意义. Camargo等[42]研究表明, 肝细胞内特异性过表达YAP会导致肝脏的体积增大, 而终止YAP的过表达则会使肝脏恢复正常大小. 值得一提的是, 持续性过表达YAP会导致肿瘤的形成[40].

相似的研究来自Kowalik等[43], 其通过TCPOBOP(1, 4-bis [2-(3, 5-dichloropyridyloxy)] benzene)诱导非转基因小鼠的肝增大, 发现YAP蛋白含量协同上升, 然而对于肝已增大的小鼠第2次注射TCPOBOP并不会进一步引起肝重增大或YAP蛋白水平提高, 这表明Hippo通路对于进一步阻止肝过度生长的作用. 也有研究敲除Hippo通路中的Mst1/2、Sav等YAP上游分子基因, 结果同样引起了肝重的增加[44-46]. 另外值得注意的是, 缺失性突变YAP 1-2个拷贝则会抑制肝重增加以及肿瘤的形成[47]. 哺乳动物细胞内YAP的主要靶基因是结缔组织生长因子(connective tissue growth factor, CTGF), 该基因对YAP诱导的细胞增殖与无支撑生长有重要作用[48]. 此外YAP/TAZ也可与Smad2/3相结合, 可能与后者的胞内定位有关[32,49].

3 ILK

ILK是整合素信号通路的主要介质, 其作为一种丝氨酸/苏氨酸激酶是细胞与其外围基质黏附的关键调节因子. ILK直接相连于整合素β1亚基的胞膜区, 包含有3个主要的功能区域, 其氨基末端含有4个锚蛋白, 对于ILK的黏着版定位, 以及对LIM调节蛋白PINCH-1、PINCH-2与ILK的结合意义重大. 位于ILK中心的普列克底物结合蛋白同源区即PH区, 是由PIP3(phosohatidylinositol 3, 4, 5-triphosphate)激活. 而ILK C端催化区所介导结构与整合素β亚基相联系, 同时连接有与肌动蛋白相连的α, β, γ三种parvin蛋白. ILK既能被整合素激活也能被生长因子诸如HGF、EGF所激活, 影响多条信号通路, 可调节细胞存活、分化、增殖、迁移以及血管生成等不同生化进程[50].

通过使用siRNA抑制ILK的表达发现, ILK的主要作用还涉及对ERK1/2, p38MAPK, JNK, 及PKB的磷酸化[51]. 除此以外, ILK作为一种丝氨酸/苏氨酸激酶, 以依赖磷脂酰肌醇激酶3(phosphatidylinositol-3-kinase, PI3K)的方式, 可磷酸化AKT第473位的丝氨酸以及GSK3β第9位丝氨酸, 从而激活前者灭活后者[50]. 值得注意的是, AKT依赖于ILK的激活主要发生在肿瘤细胞里面, 处于正常状态的细胞似乎依旧能够磷酸化AKT第473位丝氨酸[52]. ILK的转录是通过结合定位在核内ILK内含子2上的过氧化物激活受体(peroxisome proliferator-activated receptor, PPAR)反应元件, 由转录因子PPARβ所刺激. 而通过PPARβ转录所激活的ILK及PDK1反过来也能激活AKT及促进细胞存活[53]. 作为ILK第2个下游靶点, GSK3β可通过依赖于AP-1的转录激

■创新盘点

本文从细胞因子的角度, 对现阶段肝再生终止的研究进行较好的总结, 使各个因子之间的关系得以串联, 便于读者对肝再生末期各因子的作用有较为全面的认识.

■名词解释
2/3肝切除(two-thirds partial hepatectomy): 作为研究最为广泛的物理性肝损伤肝再生模型, 由Higgins和Anderson于1931年提出, 即通过外科手术将肝脏结扎并切除剩下肝叶来完成再生, 为研究肝脏再生机制提供了较为便捷完善的细胞、器官、组织模型.

活以及Cyclin D1的蛋白水解作用对细胞周期进行调控, 后者可能有赖于ILK对β-catenin转位的促进[54,55]. 此外在外源有丝分裂原的刺激研究下, 根据Donthamsetty等[56,57]的研究, 用TCPOBOP及苯巴比妥(phenobarbital, PB)分别刺激肝脏特异性敲除ILK的小鼠肝细胞, 使其增殖, 发现缺乏ILK的肝细胞能够延长其增殖期. 不论体内或是体外实验, 对肝脏特异性敲除ILK的小鼠肝细胞凋亡会有所增强, Gkretsi等[58]研究认为这是由于caspase3活性增强, 以及能够构建细胞与胞外基质黏附稳定复合物的PINCH和α-parvin表达量减少所致. 而刺激肝细胞过表达ILK则会扭转此现象.

另外根据Apte等[1]的研究, 肝特异性ILK敲除的小鼠在肝切后7 d, 再生肝重便会超过原肝重并且会进一步生长到第14天才终止, 而此时再生肝重已超过原肝重的58%. 进一步对增殖的肝细胞进行基因表达分析发现, 整合素基因表达量增加, 而与分化相关的基因表达则有所降低. 同时, 研究者认为肝切后肝重的增加主要是由HGF及其受体MET, β-catenin和Hippo通路所致. 其中ILK作用于HGF可能通过调节结合HGF的ECM.

根据Troussard等[59]的研究, 上调ILK表达量通过激活AP-1转录因子可增强金属基质蛋白酶9(matrix metalloproteinase 9, MMP9)的表达, 从而对ECM进行调节. 基质胶中, ILK也可诱导MMP-2的表达从而促进细胞的迁移及浸润[60], 而其对于β-catenin则很可能通过Wnt途径进行调节. 抑制ILK活性能直接调节Wnt信号, 通过抑制β-catenin在核上的转位及转录. 而ILK的激活则能以一种独立于PI3K的方式调节急性Wnt3a介导的β-catenin磷酸化、稳定性及核激活, 同时也延长了依赖于PI3K的Wnt信号对GSK-3的磷酸化作用[61]. ILK作用于Hippo通路也可能是通过细胞外基质的黏附所致, 有研究表明ILK可通过下调转录因子活性来调节表面黏附蛋白E-cadherin的表达[62]. ECM对于肝再生有极其重要的作用, 在肝再生过程中ECM的降解与重建是再生过程中的必要步骤. 不加胞外基质培养的肝细胞会失去肝细胞特异性基因表达模式以及细胞特有形态. ILK肝脏特异性敲除鼠能正常出生, 但在出生后不久, 通过组织学分析发现其肝叶生长异常, 肝细胞和胆管细胞生长旺盛, 且ECM降解增强[63]. 以上研究均表明了ECM可通过ILK的信号传导对于肝细胞的增殖与终止进行调节.

4 GPC3

磷脂酰肌醇3(glypican, GPC3)属于硫酸乙酰肝素糖蛋白家族成员[64]. 而GPC是一类分布在细胞膜表面的蛋白聚糖, 由核心蛋白和糖胺聚糖(GAG)侧链构成, 其羧基末端与1个糖基化磷脂酰肌醇(GPI)共价结合而连接在细胞膜上, 氨基末端游离在细胞外, 其内部有多个二硫键连接, 使其具有球形立体结构[65]. GPC3主要在肝癌细胞中表达[66], 其功能性突变会导致以过度生长及脏器骨骼发育异常为主要表型的过度生长和畸变综合征(Simpson-Gholabi-Behmel syndrome, SGB)[67]. 肝切后的小鼠肝细胞中GPC3 mRNA及蛋白水平从2 d后开始升高, 并于5 d时达到峰值, 而当肝细胞增殖速率开始降低时, GPC3依旧维持了较高的表达水平. Liu等[68]在体外试验中, 通过使用morpholino寡核苷酸抑制GPC3的表达, 发现肝细胞的生长得到促进. 进一步的酵母菌双杂交测定实验更是证明了GPC3可以干扰涉及肝细胞增殖的CD81蛋白分子作用. 同时在动物水平实验中, 通过对肝细胞过表达GPC3的转基因小鼠的研究分析, Liu等[64]也发现小鼠肝细胞的增殖率及肝切后肝再生进展均受到了抑制. 而Lin等[69]则通过PB和TCPOBOP两种异生有丝分裂原刺激转基因小鼠肝细胞增殖, 进而检测GPC3对肝细胞增殖的终止作用, 结果也证明GPC3在抑制肝细胞增殖重要性.

5 Activin

Activin是TGF-β的超家族成员, 是一种肝细胞自分泌的DNA合成抑制剂[28]. 在哺乳动物体内含量最多的是activin A, 其次是activin AB、B、C、E[70]. 其中activin C和E在肝中大量表达, 但小鼠缺乏activin C和E时, 表现为正常的肝脏发育, 肝切后再生的肝脏均表现正常[71]. 大鼠体内由腺病毒介导的activin bC亚基过表达会升高activin C含量, 进而加速肝切后肝细胞的增殖以及肝重的恢复[72], 与此相反, activin bA多在凋亡细胞中表达[73], 由此activin A常被认为是肝细胞的前凋亡因子[74], 其可抑制肝细胞DNA合成, 使肝重降低, 同时能够促进肝细胞凋亡[75]. activin A作用机制与TGF-β1基本相同, 主要依靠激活其异二聚体受体复合物(分为Ⅰ型和Ⅱ型), 激活Smad2/3引发其在细胞核上重新定位, 最终抑制肝细胞增殖[28].

activin的抑制剂主要为follistatin, 后者被认为是肝再生中的正向调控因子[76]. Kogure等[77]及Schwall等[78]的研究也证实了以上观点, 对正常小鼠注射follistatin能够诱导正常小鼠的肝细胞DNA合成, 同时在肝再生过程中也对肝细胞DNA的合成有加速作用. 肝细胞中activin A受体于肝切后24 h表达量下降而于72 h时恢复正常, 很有可能与其协调肝细胞对有丝分裂原的刺激有关[79]. 而在肝切后48 h对小鼠注射activin A也会使肝细胞增殖延长, 表明activin A对于维持正常状态下肝细胞处于G_0期的重要作用[27]; 慢性长期注射activin A则会导致大量肝细胞的凋亡[74,78]. 除以上效果通过基因修饰敲除肝中activin和inhibin的小鼠无任何其他肝异常[3]. 而通过Chabicovsky等[80]对肝内过表达activin A的转基因小鼠研究发现, activin A对肝再生过程有抑制作用, 但不会阻遏肝脏再生. 也有研究表明activin A能抑制IL-6的激活, 从而调控肝再生的进程[81].

6 IL-1

IL-1是一种由非实质细胞分泌的急性淋巴因子, 能显著抑制肝细胞的增殖[82,83]. 研究表明在肝细胞体外培养以及小鼠肝切模型实验中, IL-1β能够延迟及抑制小鼠肝切后肝细胞的增殖[83]. 同时, 也有一些研究表明IL-1α可以作为免疫反应性胰岛素(immunoreactive insulin, IRI)的介质及肝再生抑制剂[84]. 此外, IL-1受体与IL-18受体具有相同的信号调节分子-髓样分化因子(myeloid differentiation factor 88, MyD88), 其可在肝再生起始过程中作为NF-κB的激活因子[85]. 大鼠IL-1α mRNA在肝再生的前复制阶段10 h时含量开始下调, 而在24-48 h时, 即其肝细胞增殖开始乏力时, 含量会被重新上调. 从再生的肝非实质细胞中分离出来的IL-1是肝细胞DNA合成的主要抑制剂. 不管是加入IL-1R拮抗剂还是加入IL-1α和IL-1β抗体(此二抗体均是必须的)均会破坏肝再生抑制作用. 而在肝切后, 大鼠肝细胞增殖0-12 h时, 额外加入IL-1β会明显减少增殖的肝细胞[83]. 根据近几年Iimuro等[86]的研究, 失去将IL-1β和IL-18转化为活性形式的Caspase-1$^{-/-}$小鼠肝切后显示出正常的肝脏大小. 这也似乎暗示了IL-1β和IL-18在肝再生中并非具有重要作用.

7 其他因子

除以上较为广泛肝再生终止相关因子的研究, 以下因子也有涉及. 有研究者发现, 通过下调miRNA-23b可能有助于激活TGF-β1/Smad3在肝再生终止阶段信号通路[87]. 而Qin等[88]则发现, 信号调节蛋白α1(signal regulatory protein α1, SIRPα1)作为细胞增殖是一种负调节因子, 其在肝再生终止过程中也可能起重要作用. 此外有研究表明酪氨酸蛋白磷酸酶1B(protein tyrosine phosphatase 1B, PTP1B)的缺失会影响肝再生反应的触发, 同时由其调控的基因与也与肝再生终止阶段密切相关[89]. Asai等[90]的研究阐述了一种新的终止肝再生进程机制. 其研究表明再生肝细胞产生的新的神经生长因子(nerve growth factor, NGF)可能通过p75神经营养因子受体(p75 neurotrophin receptor, p75NTR)作用, 被激活后能够调控肝再生进程的肝星状细胞凋亡, 从而最终导致肝再生进程的终止. 此外也有很多研究者将目光转移到PPAR上. 由于肝再生末期脂代谢的变化, Yamamoto等[91]的研究表明PPARγ配体系统很可能对肝细胞增殖起到重要的抑制作用, 从而在肝再生终止阶段发挥重要作用. 同样, Yuan等[92]也认为肝再生末期脂代谢的增强及PPAR的激活对于肝再生终止意义重大.

8 结论

一直以来, 肝再生作为临床及再生研究的重要模型, 涉及了众多基因、细胞因子、生长因子和不同类型的细胞, 过程复杂. 其间既有受体/配体系统, 也有全身循环系统的作用. 随着肝再生起始与增殖方面的研究不断深入, 肝再生终止阶段的研究逐渐成为新的研究热点. 如何使肝再生变得可控? 如何使肝脏受损后能迅速再生且能回归到正常大小? 如何使异常增殖的肝细胞终止生长与分裂而又不影响其功能? 这些问题的解决, 不仅对肝脏移植与肝病治疗等临床治疗有深远影响, 对于探究器官组织再生研究也有重要意义. 今后对于肝再生终止阶段的研究可能更加侧重于肝ECM重建对肝细胞增殖终止的影响方面, 以及对各种已知调控机制之间的联系上. 此外, 氧压变化、脂代谢变化以及周身血供的影响也可能被更多地考虑进去.

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■同行评价
本文对肝再生终止阶段多种细胞因子与生长因子功能进行较为系统的综述, 对研究了解该方面进展有一定帮助作用.

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