

RhoA在肝纤维化发生与发展中的作用

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■背景资料

因RhoA参与调控细胞骨架、促进细胞迁移收缩,因此可以调节各器官血管内皮细胞的活动,与肺动脉高压、高血压及门静脉高压等关系密切;促进肿瘤细胞的迁移,导致恶性肿瘤转移,而RhoA对肝星状细胞活动的调节目前研究不多。

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Role of RhoA in occurrence and development of liver fibrosis

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Abstract

Liver fibrosis is a pathophysiologic process

resulting from a variety of chronic liver injuries, characterized by the excessive accumulation of extracellular matrix or the formation of scar. The transdifferentiation from quiescent hepatic stellate cells (HSCs) or portal fibroblasts (PFs) to activated myofibroblasts (MFBs) is a key step of producing extracellular matrix. RhoA can regulate the cell cytoskeleton and is involved in activating HSCs/PFs, thus having a significant fibrogenic effect. In this paper, we review the recent advances in understanding the role of RhoA in the occurrence and development of liver fibrosis.

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Key Words: RhoA; Liver fibrosis; Hepatic stellate cells; Portal fibroblasts; Myofibroblasts

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摘要

肝纤维化是由各种慢性肝损害所导致的病理过程,主要表现为大量的细胞外基质沉积或瘢痕形成。肝星状细胞(hepatic stellate cells, HSCs)以及门脉成纤维细胞(portal fibroblasts, PFs)向肌成纤维细胞(myofibroblasts)转化,是生成细胞外基质的关键步骤。RhoA主要功能是调控细胞骨架,参与了HSCs/PFs活化的调节,具有明显的促纤维化作用。本文就该信号通路在肝纤维化发生、发展中作用的研究进展作一综述。

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关键词: RhoA; 肝纤维化; 肝星状细胞; 门脉成纤维细胞; 肌成纤维细胞

核心提示: 目前许多研究表明肝星状细胞或门脉成纤维细胞向肌成纤维细胞的转化是肝纤维化发生的关键。研究RhoA对肝星状细胞或门脉成纤维细胞的调控机制有望进一步阐明肝纤维化发生的机制, 为抗纤维化找到新的分子靶点。

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0 引言

肝纤维化是肝脏应对各种慢性肝损害因子的损伤修复反应, 伴随肝内持续大量的细胞外基质沉积, 纤维瘢痕的形成及肝脏结构的改变, 并最终导致肝硬化甚至肝癌^[1-3]。其中, 静止型肝星状细胞向增殖型肌成纤维细胞的转化是肝纤维化发病的中心事件^[1]。另外, 门脉成纤维细胞也可以向肌成纤维细胞转化^[1,4]。增殖型肌成纤维细胞特异性表达 α 平滑肌肌动蛋白(α -smooth muscle actin, α -SMA)为细胞骨架的主要成分之一, 引起细胞形态的改变^[5,6], 而RhoA作为调节肌动蛋白细胞骨架的关键分子^[7], 参与了对HSCs和PFs活化的调控^[8], 因此, RhoA在肝纤维化的发生发展中扮演重要角色。

1 RhoA

在Rho GTP酶超家族已发现超过20个成员, 其中, RhoA、Rac1和Cdc42是目前研究最多的Rho GTP酶^[9,10]。鸟苷酸交换因子(guanine nucleotide exchanging factors, GEFs)、GTP酶活化蛋白(GTPase activating protein, GAP)和GDP解离抑制因子(GDP dissociation inhibitor, GDI)共同调节Rho家族蛋白在活性型和失活型构象之间转换^[11-13]。Rho GTP酶是细胞内多条信号转导通路的关键分子, 活化的Rho GTP酶可参与肌动蛋白骨架、细胞极性、细胞黏附、内吞作用、细胞形态形成、胞浆移动、基因转录、G₁细胞周期、微管动力学、囊泡运输、酶活

化、细胞增殖和凋亡的调节, 并与肿瘤的发生和转移密切相关^[10,11,14]。RhoA通过调节肌动蛋白张力纤维和肌球蛋白收缩调节细胞骨架。张力纤维由肌动蛋白、肌球蛋白、原肌球蛋白等组成, 与细胞间或细胞与基质表面的黏着有密切关系^[15], 且肌动、肌球蛋白相对运动产生的收缩力是细胞迁移动力的主要来源^[16]。

2 RhoA与肝纤维化

当GEFs磷酸化后, RhoA从GDP结合向GTP结合的构象转变, RhoA活化^[14], 激活的RhoA可通过以下途径调节肝纤维化: 首先, 在肝脏血管平滑肌细胞(vascular smooth muscle cells, VSMCs)中, RhoA一方面激活其下游的Rho相关卷曲螺旋形成蛋白激酶1(Rho associated coiledcoil forming protein kinase 1, ROCK1)可抑制肌球蛋白轻链磷酸酶(myosin light chain phosphatase, MLCP)的活性, 提升肌球蛋白轻链(myosin light chain, MLC)的磷酸化水平, 增加肌动-肌球蛋白的收缩力, 血管平滑肌细胞收缩增强^[17,18], 另一方面, ROCK2激活LIM激酶(LIM-kinase, LIMK), 抑制球状肌动蛋白(globular actin, G-actin), 解聚纤维状肌动蛋白(fibros actin, F-actin), 导致肌动蛋白重组, 促进细胞运动和收缩, RhoA还可以增加VSMCs对钙离子的敏感性及调节下游血清反应因子(serum response factor, SRF)的活化, 增加并维持血管平滑肌的收缩, 使肝血管抵抗增加^[14,19]; 此外, 活化的RhoA使内皮细胞功能紊乱, 负性调控eNOS的功能, 导致舒血管物质NO减少, 血管收缩增强^[20,21], 上述效应使门静脉压力增高, 肝硬化加重。最近研究也表明, RhoA还可以通过调控HSCs的活化参与肝纤维化的调节。

2.1 RhoA加速HSCs/PFs的活化 HSCs和PFs向MFBs转化后大量增殖, 产生细胞外基质(extracellular matrix, ECM), 合成I型胶原, 特异性表达 α -SMA, 并获得收缩、黏附及迁移能力^[22]。HSCs的活化伴随于细胞骨架的改变, 作为细胞骨架主要组成成分之一的肌动蛋白是引起细胞骨架改变的关键, 随着 α -SMA的增加, G-actin单体向F-actin多聚体转化, 细胞骨架的重组是驱使细胞活化的主要动力^[8,23], Cui等^[5]通过张力纤维形成评估肌动蛋白细胞骨架发现, 给予HSC-T6细胞jasplakinolide(Jas)(诱

■ 研究前沿

目前对于肝纤维化发生发展的机制中的信号网络的研究很多, 肝星状细胞(hepatic stellate cells, HSCs)活化是肝纤维化发生的关键, 且肝纤维化的发生与多种信号网络的相互调节有关。但抗肝纤维化仍缺乏突破性药物, 因此在研究肝纤维化发病机制的同时需探讨肝纤维化潜在的治疗靶点。

■ 相关报道

研究发现RhoA可以使血管平滑肌细胞和内皮细胞功能紊乱, 导致多个器官的生理功能紊乱。这些研究都比较明确地阐述将RhoA对这两种细胞的调控机制, 且有许多关于RhoA抑制剂治疗疾病的报道, 此外RhoA还通过调控HSCs/门脉成纤维细胞(portal fibroblasts, PFs)/肌成纤维细胞(myofibroblasts, MFBs)参与纤维化的调节。

■ 创新盘点

HSCs/PFs的活化是肝纤维化发生的关键, 本文综述了RhoA加速HSCs/PFs活化, 促进HSCs/PFs迁移、黏附及收缩, 促进肌成纤维细胞的增殖、抑制其凋亡的机制。

导肌动蛋白聚合成F-actin)处理后, α -SMA和I型胶原表达上调; 然而给予细胞松弛素D(cytochalasin D, Cyto D)(促使F-actin解聚)处理后, HSC-T6细胞形态完整, 因此F-actin细胞骨架与HSCs的活化密切相关。而RhoA直接参与调控细胞骨架^[24], 由上可以认为RhoA参与调控HSCs及PFs的活化。

2.2 RhoA促进HSCs/PFs迁移、黏附和收缩 越来越多的证据表明, HSCs/PFs向纤维化区域的迁移和集聚是肝纤维化发生的首要步骤^[25,26]。作为一个重要的细胞过程, 细胞迁移参与了众多生理活动, 包括: 胚胎发生、伤口愈合、炎症及组织再生, 尤其在癌症细胞的浸润和转移中发挥关键作用。细胞迁移通常发生在化学引诱物或趋化因子出现在细胞周围后, 这一过程也称为趋化性^[14]。当HSCs或PFs向MFBs转化后, MFBs周围ECM, 各种细胞因子如白介素-6(interleukin-6, IL-6)、肿瘤坏死因子 α (tumor necrosis factor α , TNF- α)、单核细胞趋化蛋白-1(monocyte chemotactic protein 1, MCP-1)等及各种生长因子如转化生长因子- β 1(transforming growth factor β 1, TGF- β 1)、成纤维细胞生长因子(fibroblast growth factor, FGF)、血小板源性生长因子(platelet derived growth factor, PDGF)、表皮生长因子(epidermal growth factor, EGF)、肝细胞生长因子(hepatocyte growth factor, HGF)、血管内皮生长因子(vascular endothelial growth factor, VEGF)等分泌增加^[27], ECM、细胞因子及生长因子作为化学引诱物又将导致更多的细胞向其迁移^[28], 这一恶性循环及ECM、细胞因子和生长因子间的共同作用导致纤维化相关基表达上调, 基质金属蛋白酶(matrix metalloproteinases, MMPs)及基质金属蛋白酶类组织抑制剂(tissue inhibitor of matrix metalloproteinases, TIMPs)代谢失调, ECM逐渐沉积, 胶原生成增加, 最终形成肝纤维化^[29,30]。此外, RhoA与核因子- κ B(nuclear factor- κ B, NF- κ B)相互作用共同加重细胞炎症^[31], 而RhoA/ROCK抑制剂可以直接抑制炎症因子IL-6、TNF- α 、MCP-1的表达^[32-34], 趋化因子生成减少, 间接地使细胞迁移减少。而肌动蛋白细胞骨架改变是细胞迁移的关键^[35], 因此RhoA可以直接参与细胞迁移的调控。此外, 随着肌动蛋白的增加, 大量F-actin聚集形成张力纤维, 张力纤维和黏着斑相互作用共同调节细胞的黏附^[26]。另有研究^[14]发

现, RhoA的活化可以稳定黏着斑黏附于ECM, 细胞黏附于ECM可以激活Rac1和Cdc42, 进而促进细胞迁移。同时细胞收缩能力也是影响细胞运动的主要因素之一。在细胞迁移时, 细胞体后缘脱离胞体, 同时引起细胞收缩, 进而使细胞向前移动。Klein等^[36]利用3D压力松弛胶原晶格收缩模型发现, Janus激酶2(Janus kinase 2, JAK2)可通过激活RhoA/ROCK信号通路, 参与调节HSCs的收缩; Liu等^[37]利用3D压力松弛胶原晶格收缩模型同样发现, RhoA/Rho激酶的活化可以使HSCs收缩增强。

2.3 RhoA促进MFBs增殖, 抑制MFBs凋亡 在真核细胞中, 细胞周期的调节主要依赖于细胞周期蛋白(cyclins), 细胞周期蛋白依赖激酶(cyclin-dependent protein kinases, CDKs)及细胞周期蛋白依赖激酶抑制因子(cyclin-dependent protein kinases inhibitor, CKIs)等。作为CKIs家族中一员的P27在调节细胞增殖方面起重要作用, 调控细胞周期G₁向S期的转化, RhoA通过下调P27, 阻碍G₁向S期转化的进程, 抑制活化型HSCs的增殖, 并促进其凋亡, RhoA负性调控细胞增殖^[38,39]。RhoA的异常活化可以直接抑制CDKs的活性, 抑制细胞凋亡, 延长细胞生命周期^[14]。HSCs活化过程中, 除了肌动蛋白细胞骨架成分增加之外, 肌动蛋白丝结合蛋白-豆蔻酰化的富含丙氨酸的蛋白激酶C的底物(myristoylated alanine-rich kinase C substrate, Marcks)也增加, 且Marcks在活化HSCs的迁移、收缩及增殖中起重要作用, 干扰Marcks可以阻断细胞骨架重组, 进而抑制HSCs的增殖^[40,41]。细胞信号转导中G蛋白偶联受体(G protein-coupled receptor, GPCR)的配体凝血酶、溶血磷脂酸(lysophosphatidic acid, LPA)、1-磷酸鞘氨醇(sphingosine-1-phosphate, S1P)和血栓素A2(thromboxane A2, TXA2)可以活化RhoA, 刺激多种细胞和组织的增殖、分化和炎症。RhoA还通过调节转录因子激活蛋白1(activator protein-1, AP-1)、NF- κ B、Yes相关蛋白(Yes-associated protein, YAP)及心肌相关转录因子A(myocardin-related transcription factor, MRTF-A)基因表达影响细胞增殖^[42,43]。RhoA通过调节磷脂酰肌醇3激酶(phosphatidylinositol 3-kinase, PI3K)、黏着斑激酶(focal adhesion kinase, FAK)、丝氨酸-苏氨酸蛋白激酶B(serine/threonine protein kinase

B, AKT)、同源性磷酸酶-张力蛋白(phosphatase and tensin homolog, PTEN)促进细胞生存^[44,45]. MFBs的凋亡是肝脏清除纤维瘢痕的内源性反应. 研究^[46]表明RhoA参与调控心肌成纤维细胞(cardiac fibroblast, CFs)和心肌成纤维细胞(cardiac myofibroblast, CMFs)凋亡的调节, 给予RhoA抑制剂肉毒杆菌C3胞外酶处理后CFs和CMFs凋亡增加.

3 RhoA/ROCK信号通路与抗肝纤维化

大量体外研究表明肉毒杆菌C3胞外酶、耶尔森氏菌外膜蛋白T(Yersinia outer protein T, YopT)和耶尔森氏菌外膜蛋白E(Yersinia outer protein E, YopE)可以使RhoA失活, 活化的RhoA还可以通过E3泛素连接酶Smurf1或多聚体E3泛素连接酶复合体SCF-BACLRD进行降解, *RhoA*基因敲除或基因干扰后, RhoA表达同样下调^[10], HSCs中转染显性失活突变的RhoA(DN-RhoA)后, RhoA促HSCs分化的作用明显减轻^[47]. 予Y27632阻断RhoA下游ROCK信号分子后, RhoA的促肝纤维化效应同样被阻断^[48], 体内研究^[49]发现靶向给予HSCs甘露糖-6-磷酸修饰人血清白蛋白携带的Y26732后, 肝纤维化同样减轻. 他汀类药物可抑制胆固醇合成的关键酶3-羟基-3-甲基戊二酰单酰辅酶A还原酶(HMG)-CoA的活性, 抑制胆固醇生物合成过程中类异戊二烯中间产物的生成, 这些中间产物包括甲羟戊酸、法尼基焦磷酸(farnesyl pyrophosphate, FPP)和香叶基焦磷酸香叶酯(geranylgeranyl pyrophosphate, GGPP), 这些产物为RhoA蛋白翻译后修饰所必需, 因此他汀类药物可以阻止RhoA的活化, 阻断PFs向MFBs的转化, 并抑制MFBs的增殖, 加速MFBs的凋亡^[46,50]. 另有研究^[37,51]表明阿魏酸钠同样可以通过减少GGPP的生成, 阻断RhoA的活化, 使HSCs收缩减轻, 凋亡增加, 减轻继发性胆汁性肝硬化导致的门静脉高压. 纤溶酶原激活物抑制剂1(plasminogen activator inhibitor 1, PAI-1)可以使纤维蛋白沉积增加, 纤维化加重, PAI-1缺乏的小鼠肺纤维化明显减轻, 法舒地尔可以阻断RhoA/ROCK信号通路的活化, 部分抑制PAI-1进而加速纤维蛋白的降解, 减轻纤维化^[52,53].

4 结论

RhoA与肝纤维化的发生与发展密切相关, 目

前对于肝纤维化仍缺乏突破性药物, RhoA在肝纤维化中的研究为我们提供了潜在的治疗靶点. 特异性阻断RhoA及其下游ROCK分子已被大量证实可以减轻肝纤维化基因的表达, 然而目前仍缺乏RhoA特异性抑制剂用于体内抗肝纤维化的证据, 因此研究RhoA及其阻断剂对肝纤维化的作用, 将为肝纤维化的治疗带来新的方向.

应用要点

RhoA与肝纤维化的发生、发展密切相关, 目前治疗肝纤维化仍缺乏突破性药物, RhoA在肝纤维化中的研究为研究者提供了潜在的治疗靶点. 研究RhoA及其阻断剂对肝纤维化的作用, 将为抗肝纤维化带来新的方向.

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■名词解释

MFB: 肌成纤维细胞, HSC/PF活化后的表型, 具有增殖的特性, 其增殖促进肝纤维化的发生发展。

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同行评价

本文层次较为清晰, 选题较为新颖, 把握了肝纤维化研究的热点问题, 学术价值较好, 对研究肝纤维化发生发展的分子机制有一定指导意义。

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