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文献综述 REVIEW

ROCK抑制剂Y-27632对TGF-β1/CTGF通路的影响

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■背景资料
肝纤维化是多种原因引起的慢性肝损害所致的病理改变, 表现为肝内细胞外间质成分过度异常地沉积, 并影响肝脏的功能, 是慢性肝病发展到肝硬化必经之阶段. 现认为肝纤维化尚有逆转至正常的可能, 目前研究的重点放在分子与分子、分子与细胞及细胞与细胞间的相互作用方面.

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Effects of ROCK inhibitor Y-27632 on TGF-β1/CTGF pathway

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Abstract
Y-27632, a pyrimidine derivative, is a recently developed synthetic specific inhibitor of Rho associated coiled-coil forming protein kinase (ROCK), and it inhibits the process of hepatic fibrosis by regulating a variety of biological effects mediated by ROCK. Recent studies have found that the transforming growth factor β1 (TGF-β1)/connective tissue growth factor (CTGF) signaling pathway is involved in liver fibrosis. TGF-β1 induces the expression of its downstream molecule CTGF, resulting in the increase of extracellular matrix and liver fibrosis. Y-27632 can inhibit the expression of TGF-β1 and CTGF. This paper attempts to explain the anti-fibrosis effect of Y-27632 in terms of the impact of Y-27632 on the TGF-β1/CTGF pathway, with an aim to better understand the functional target of Y-27632 and provide a theoretical basis for the targeted therapy of liver fibrosis.

Key Words: ROCK inhibitor; Y-27632; Liver fibrosis; Transforming growth factor β1; CTGF

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摘要
Y-27632为嘧啶衍生物, 是一种近年来合成的特异性Rho相关螺旋卷曲蛋白激酶(Rho associated coiled-coil forming protein kinase, ROCK)抑制剂, 能通过调控ROCK介导的多种生物效应从而抑制肝纤维化的形成. 研究发现, 转化生长因子β1(transforming growth factor β1, TGF-β1)/结缔组织生长因子(connective tissue growth factor, CTGF)通路参与肝纤维化的形成, TGF-β1诱导其下游效应分子CTGF表达, 促使细胞外基质生成增多, 导致肝纤维化. Y-27632具有抑制TGF-β1和CTGF表达的作用, 本文从ROCK抑制剂Y-27632对TGF-β1/CTGF通路的影响来阐述Y-27632的抗纤维化作用, 借此更深入的了解Y-27632的作用靶点, 为肝纤维化的靶向治疗提供理论依据.

关键词: ROCK抑制剂; Y-27632; 肝纤维化; 转化生长因子β1; 结缔组织生长因子

核心提示: 目前, Rho相关螺旋卷曲蛋白激酶(Rho associated coiled-coil forming protein kinase, ROCK)抑制剂Y-27632已成为新药研发的热点, 许多研究已证实了Y-27632能有效阻断转化生长

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因子β1(transforming growth factor β1, TGF-β1)/结缔组织生长因子(connective tissue growth factor, CTGF)通路, 在细胞迁移、基质代谢与细胞因子调节等方面改善肝纤维化, 因此, 本文就ROCK抑制剂Y-27632对TGF-β1/CTGF通路的影响机制作一综述.

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0 引言

肝纤维化是一个多因素参与的复杂的病理过程, 其中心环节是肝星状细胞(hepatic stellate cell, HSC)的活化. 在各种损伤因子刺激下, HSC从静止状态活化为肌成纤维样细胞并产生大量细胞外基质(extracellular matrix, ECM), 促进肝纤维化的形成[1-3]. 研究表明, 转化生长因子(transforming growth factor β1, TGF-β1)是促使HSC活化最重要的细胞因子[4-6], 结缔组织生长因子(connective tissue growth factor, CTGF)是TGF-β1下游效应因子, 主要作用为刺激细胞增生和ECM合成, 介导TGF-β1促进组织器官纤维化方面的生物学效应. 近年来, 靶向阻断TGF-β1及相关信号通路治疗肝纤维化受到学者广泛关注[7-9]. 而在肝纤维化动物模型实验中, 经Rho相关螺旋卷曲蛋白激酶(Rho associated coiled-coil forming protein kinase, ROCK)抑制剂Y-27632治疗后的动物肝纤维化得到明显改善[10], 因此, 本文就ROCK抑制剂Y-27632对TGF-β1/CTGF通路的影响作一综述.

1 Rho激酶抑制剂Y-27632的生物学效应及分子机制

Rho/ROCK信号通路是近年来较深入研究的与纤维化密切相关的通路, 其过度激活参与肺、心、肝、肾等纤维化[11-14]. Rho/ROCK信号通路通过促进肌动蛋白微丝骨架的聚合, 调控着平滑肌细胞的收缩、黏附、迁移、增殖和凋亡等多种生物学行为和功能[15,16]. Rho/ROCK信号通路的关键信号分子包括Rho GTP酶(Rho GTPase)、ROCK以及肌球蛋白磷酸酶(myosin phosphatase, MP), 其中ROCK是Rho的下游效应分子, 属于丝氨酸/苏氨酸蛋白激酶家庭成员[17,18]. Y-27632, 一种二盐酸化穿膜小分子, 化学式$C_{14}H_{23}C_{l2}N_3O$, 通过与ROCK竞争性结合腺嘌呤核苷三磷酸(adenosine triphosphate, ATP)特异性的抑制ROCK[19,20]. 目前, Y-27632已广泛用于研究ROCK在细胞和动物模型中生物学特性[21,22]. Masamune等[23]研究表明, Y-27632能作用于活化的胰腺星状细胞, 使应力纤维解体并抑制α-平滑肌肌动蛋白(α-smooth muscle actin, α-SMA)表达, 对肌动蛋白细胞骨架有调节作用. Roberts[24]发现, Y-27632能提高肌球蛋白轻链磷酸酶(myosin light chain phosphatase, MLCP)活性, 使MLC磷酸化增多, 从而导致细胞变形能力减弱、平滑肌细胞张力减小. Bishop等[25]实验证实, Y-27632能有效抑制肝癌细胞的迁移活动和侵袭能力, 减少转移灶的出现. Ikeda等[26]发现, Y-27632能抑制腺嘌呤二核苷酸磷酸氧化酶活性, 并上调半胱氨酸蛋白酶-3(Caspase3)表达, 从而诱导HSC凋亡, 缓解肝纤维化. 总之, Y-27632或通过调控细胞骨架重排过程来抑制HSC活化和迁移, 虽然Y-27632的安全性尚待量化评估, 但对其进一步研究将为临床治疗肝纤维化提供了重要理论依据.

2 TGF-β1/CTGF通路在肝纤维化中的作用

TGF-β1和CTGF是HSC重要的活化因子, 但目前国内外关于TGF-β1/CTGF通路在肝纤维化中的作用的研究尚为少见, 对于TGF-β1通过何种方式诱导CTGF产生尚不明确. TGF-β1激活其受体后, 通过磷酸化Smads将胞质内信号传递到细胞核内, 从而实现对靶基因的调控, 参与成纤维细胞的增殖、细胞表型转化和细胞外基质合成等纤维化过程[27,28]. CTGF是一种分泌性蛋白, 参与调节细胞增殖、分化、黏附和迁移等多种细胞功能, 在肝实质细胞、HSC、胆管上皮细胞及肌成纤维细胞均有表达. 更为重要的是, CTGF作为TGF-β1的下游效应分子, 协同加强了TGF-β1组织重构和促纤维化效应[29,30]. 研究发现, CTGF在正常肝组织中表达较低, 而在肝纤维化患者和肝纤维化动物模型中表达较高[31,32], 这提示或通过特异性抑制CTGF表达从而延缓或逆转肝纤维化的进程. 对于TGF-β1如何诱导CTGF产生, 研究学者认为, TGF-β通过TGF-β/TβR/Smads信号转导通路, 形成Smads2、Smads3、Smads4复合物后进入细胞核, 并与细胞核内转录因子共同作用, 激活*CTGF*基因启动子序列上位于-162--128 bp处的TGF-β反应原件, 从而诱导CTGF的表达[33,34]. 还有部分

■研发前沿

Y-27632为嘧啶衍生物, 是一种近年来合成的特异性Rho相关螺旋卷曲蛋白激酶(Rho associated coiled-coil forming protein kinase, ROCK)抑制剂, 能通过调控ROCK介导的多种生物效应从而抑制肝纤维化的形成. 转化生长因子β1(transforming growth factorβ1, TGF-β1)和结缔组织生长因子(connective tissue growth factor, CTGF)是肝星状细胞(hepatic stellate cell, HSC)重要的活化因子, 对于TGF-β1通过何种方式诱导CTGF产生尚不明确.

■相关报道

目前已有研究报道, Y-27632使细胞变形能力减弱、张力减小从而有效抑制肝癌细胞的迁移活动和侵袭能力, 减少转移灶的出现. Y-27632或通过调控细胞骨架重排过程来抑制HSC活化和迁移, 诱导HSC凋亡, 从而缓解肝纤维化.

■创新盘点
目前, 国内外关于TGF-β1/CTGF通路在肝纤维化中的作用的研究尚为少见, Y-27632的应用尚有局限性. 本文针对ROCK抑制剂Y-27632对TGF-β1/CTGF通路的影响机制进行阐述具有一定的创新性.

学者认为, TGF-β1通过激活其他信号分子诱导CTGF表达, 如细胞外调节蛋白激酶1/2(extracellular regulated protein kinases, Erk1/2), 胞质酪氨酸激酶(janus kinase, JAK)/信号转导子和转录激活子(signal transducer and activator of transcription, STAT), 氨基末端激酶(c-Jun N-terminal kinase, JNK), P38丝裂原激活蛋白激酶(mitogen activated protein kinase, MAPK), 蛋白激酶C(protein kinase C, PKC)和磷脂酰肌醇3-激酶(phosphatidylinositol 3-kinase, PI3K)/蛋白激酶B(protein kinase B, PKB或者Akt). Liu等[35]研究表明, TGF-β1通过激活JNK/STAT通路, 诱导STAT3磷酸化. STAT3作为介导下游CTGF表达的重要分子与Smads3参与整个TGF-β1/CTGF通路的调控. 另有研究表明, PI3K/Akt信号通路虽能调控STAT3磷酸化[36,37], 但却对CTGF表达无影响[38], 这提示或存在除STAT3之外的通路或分子参与TGF-β1/CTGF通路. 总而言之, TGF-β1/CTGF通路参与了肝纤维化的发生、发展[38,39], 明确TGF-β1/CTGF通路的具体机制可为以该通路为靶向治疗肝纤维化带来新的突破.

3 ROCK抑制剂Y-27632对TGF-β1/CTGF通路的影响

Zhu等[40]在研究人类视网膜色素上皮细胞试验中发现, TGF-β1/CTGF通路与Rho/ROCK通路存在串扰(crosstalk), 且TGF-β1/CTGF通路能够激活Rho/ROCK通路使纤连蛋白大量表达. Muehlich等[41]证实, RhoA和血清反应因子(serum response factor, SRF)的过度表达促使CTGF显著表达, 这提示CTGF与Rho/ROCK通路相联系. 大量研究证实, CTGF参与了Rho/ROCK通路介导的细胞增殖、分化、凋亡, 且由ROCK直接介导[42,43]. 此外, 沉默*CTGF*基因能抑制肝组织中α-SMA表达, 阻止HSC的活化, 这一发现与Y-27632显著抑制α-SMA表达的结果相同[44,45], 提示ROCK抑制剂的抗纤维化作用可能涉及TGF-β1/CTGF通路. Hu等[46]研究发现, ROCK抑制剂不仅能阻止TGF-β1诱导的上皮细胞-间质转分化(epithelio-mesenchymal interaction, EMT), 还能抑制TGF-β1介导的胶原Ⅰ和CTGF表达. 由于Smads3参与TGF-β1/CTGF通路的调控, Chen等[47]研究发现, Smads3与苏氨酸蛋白激酶(P21-activated kinase 1, Pak1)相互关联, 抑制Pak1激活可抑制Smads3激活. 采用小分子干扰RNA(small interfering RNA, siRNA)技术下调Pak1的表达能抑制Smads3反应性荧光素酶p3TP-lux和CAGA12-luc激活. 值得一提的是, TGF-β1能显著诱导p3TP-Lux基础启动子活性, 且报告基因CAGA12-luc能反映TGF-β1的转录活性, 而Wang等[48]发现, RhoA活化后能上调Pak1, 即Pak1活性受ROCK调节, 这提示ROCK抑制剂Y-27632或通过间接抑制Smads3表达从而阻断TGF-β1/CTGF通路, 达到缓解肝纤维化的效果.

■应用要点
由于Y-27632能有效阻断TGF-β1/CTGF通路, 在细胞迁移、基质代谢与细胞因子调节等方面改善肝纤维化, 因此, 阐明Y-27632在TGF-β1/CTGF通路上的作用靶点将有助于为肝纤维化的有效治疗确定新的治疗原则.

4 结论

目前, ROCK抑制剂已成为新药研发的热点, 许多研究已证实了Y-27632的用途及其治疗价值[49-51]. 由于Y-27632能有效阻断TGF-β1/CTGF通路, 在细胞迁移、基质代谢与细胞因子调节等方面改善肝纤维化[45], 因此, 阐明Y-27632在TGF-β1/CTGF通路上的作用靶点将有助于为肝纤维化的有效治疗确定新的治疗原则.

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■**名词解释**
α-平滑肌肌动蛋白(α-SMA): 一种中等大小的蛋白质, 由375个氨基酸残基组成, 并且是由一个大的、高度保守的基因编码. 真核细胞需要肌动蛋白纤维网络来控制并维持其形态及内部构造.

■同行评价
TGF-β1和CTGF均为致肝纤维化的重要炎症因子, Rho/ROCK信号通路与HSC的活化具有密切关系. 本文从逻辑上将以上三者有机的组合在一起, 具有重要意义. 本文书写流畅, 具有较好的文字功底, 逻辑性强.

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