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文献综述 REVIEW

肝星状细胞激活与信号转导

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Signal transduction and activation of hepatic stellate cells

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Abstract
Liver fibrosis, which leads to cirrhosis, occurs as a result of various injurious processes and it is the common pathologic basis of all the chronic hepatic diseases. At present, a good many researches demonstrate that the activation of hepatic stellate cells play a critical role in fibrogenesis. Prolonged liver injury results in hepatocyte damages and secretion of many fibrogenic cytokines such as transforming growth factor-beta 1, angiotensin, and leptin, which triggers the activation of hepatic stellate cells through different intracellular signal transduction pathways. In this article, we reviewed the research advancement in the signal transduction pathway of nuclear receptor and membrane receptor during the activation of hepatic stellate cells.

Key Words: Hepatic stellate cell; Signal transduction; Activation; Liver fibrosis

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摘要
肝纤维化是多种慢性肝病向肝硬化发展的必经阶段, 是所有慢性肝病的共同病理基础. 目前认为肝星状细胞的激活是肝纤维化形成的关键, 各种致病因素作用下引起肝损伤, 释放多种细胞因子, 如转化生长因子β、血管紧张素、瘦素, 通过各种信号转导使肝星状细胞激活. 本文就肝星状细胞激活过程中一些重要的膜受体、核受体信号转导途径及其研究进展作一综述.

关键词: 肝星状细胞; 信号转导; 激活; 肝纤维化

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■背景资料
肝纤维化是慢性肝病重要的病理特征, 也是肝硬化发生的前奏和必经中间环节, 其中肝星状细胞的激活又是肝纤维化形成的关键, 近年来对肝星状细胞激活的各种信号转导途径进行了深入的研究, 干扰其主要的信号转导途径为肝纤维化治疗带来了新的曙光.

0 引言
肝纤维化是各种慢性肝病向肝硬化发展的必经阶段, 是所有慢性肝病的共同病理基础[1-2]. 目前认为, 在各种致病因素作用下, 肝细胞、Kupffer细胞、内皮细胞、肝星状细胞(HSC)等可产生多种细胞因子、氧化应激活性产物等[3-4], 这些细胞因子通过各种信号转导途径介导HSC的激活是肝纤维化形成的关键[5-7]. 近年来, 国内外学者对HSC激活的信号转导途径进行了深入的研究, 干扰HSC激活过程中信号途径已成为治疗肝纤维化的热点[8-10]. 我们就HSC激活过程中一些重要的膜受体信号途径、核受体信号转导途径及其研究进展作一综述.

1 肝星状细胞激活与膜受体信号转导途径
在肝纤维化形成过程中, 转化生长因子β(TGFβ)、血小板衍生生长因子(PDGF)、瘦素(leptin)、血管紧张素(AngⅡ)等是致HSC活化主要的细胞因子, 他们必须与相应膜受体结合后方可将信号传递至细胞内相应的效应分子, 调节细胞的功能.

1.1 TGFβ受体介导的信号转导途径 TGFβ是促进HSC激活和细胞外基质的合成的主要细胞因子之一[11], 其中TGFβ1的活性最强, TGFβ受体属于单次跨膜受体, 人类细胞普遍存在TGF的

■研发前沿
近年就阻断肝星状细胞中的信号转导途径成了研究的热点，如TGFβⅡ型可溶性受体, PPAR-γ配体等用于肝纤维化的防治, 但其安全性有待深入研究.

3种类型受体, 其中TGFβ1与Ⅱ型受体亲和力最高, TGFβ1先与跨膜蛋白Ⅱ型膜受体结合成膜外复合物, 再与Ⅰ型膜受体结合形成Ⅱ型受体-TGFβ1-Ⅰ型受体复合物, 活化的受体催化一类重要的信号分子smad发生丝氨酸磷酸化, smad分子形成同源或异源寡聚体后进入细胞核, 调节相应基因的转录[12], 其中smad2, smad3属于受体调节型smads(R-smads)[13-14], 而smad6, smad7属于抑制型smads(I-smads)[15], Schnabl *et al*[16]在对smad3基因敲除小鼠的研究中发现, 与野生型小鼠比较, 基因敲除组小鼠肝中α1(Ⅰ), α2(Ⅱ)mRNA表达分别下降58%, 36%, 但并不影响α-SMA和desim的表达, 进一步发现, smad3缺陷的HSC无TGF-β诱导的smads复合物生成及向细胞核内转位产生转录效应, 没有smads复合物生成, TGF-β1无法诱导HSC活化及合成细胞外基质. Dooley *et al*[17]构建了smad7基因重组腺病毒载体(AdSmad7), 并分别从尾静脉和门静脉导入胆管结扎(BLD)致肝纤维化动物模型体内, 与AdLacZ组比较, 导入AdSmad7的BLD大鼠肝组织中的Ⅰ型胶原, 羟脯氨酸均下降, 体外研究发现, 转染了AdSmad7的HSC继续保持静息状态, 提示smad7的表达上调阻滞原代肝星状细胞的转型, 但并不影响α-SMA的表达. smad7干扰TGF信号转导机制可能是通过抑制smad2/smad3磷酸化、活性smad复合物的核转位及(CAGA)(9)-MLP-Luc的激活. 近年发现, TGFβ也可以通过p38MAPK、胞外信号调节激酶(ERK)、氨基端激酶(JNK)信号途径调节HSC的生物学行为[18], Tsukada *et al*[19]发现, TGF-β1分别通过Smad和p38MAPK独立的调控α1(Ⅰ)基因的表达, 但是二者的作用是可以叠加, 深入研究表明, TGFβ是通过p38MAPK信号途径, 而并非通过Smad途径增加α1(Ⅰ)mRNA的稳定性, 同时阻断这二条信号途径几乎完全抑制α1(Ⅰ)胶原基因的表达. Yoshida *et al*[20]研究急性肝损伤过程中TGFβ1、PDGF通过激活JNK途径调节smad2/3连接区的磷酸化, 同时JNK途径可能介导HSC由disse间隙向组织损伤处的迁徙, JNK途径特异性抑制剂SP600125可以阻滞HSC的迁徙. 目前许多研究表明, 干扰TGF信号途径是治疗肝纤维化的有效方法[21-24], 如 Nakamuta *et al*[25]把可表达TGFβⅡ型可溶性受体的质粒转染到实验性肝纤维化大鼠的骨骼肌细胞, 1 wk后在血清中可检测到该受体的稳定表达, 转染组肝纤维化程度减轻, 肝组织中羟脯氨酸, Ⅰ型胶原, α-SMA表达下降, 同时还可以调节Th1/Th2细胞因子平衡, 表现为肝组织中IL12下降, 而IL10表达升高. TGFβ是至肝纤维化的一重要因子, 深入研究其介导的信号途径及生物学作用对肝纤维化防治具有十分重要的意义.

1.2 PDGF受体介导的信号转导途径 PDGF是sis原癌基因表达产物, 是已知促HSC增殖作用最强的细胞因子, PDGF在肝脏中主要由血小板, kupffer细胞, 窦内皮细胞产生, PDGF受体属蛋白酪氨酸激酶受体家族, 有α、β两种亚型, PDGF结合到HSC胞膜上的受体后, 再通过PI3-K途径、STAT途径、Ras/TPK途径、钙通道途径、Na^+/H^+途径、PLC-γ1途径从而促进HSC的增殖、激活[26-27]. 近年来在对PDGF受体介导的信号转导途径研究中有许多新的发现, Breitkopf *et al*[28]研究了在静息的HSC向肌成纤维细胞过程中PDGF-A、-B、-C、-D各亚型的表达情况, PDGF-A mRNA仅出现微量的波动, PDGF-B在HSC激活的第3天表达已经明显下降, 而C型, D型是新发现的PDGF亚型, 在此过程中表达分别升高5倍和8倍, 且持续较长时间, 表明在HSC激活的早期主要通过PDGF-B介导信号转导, 后期则通过C型, D型介导的. Adachi *et al*[29]和Kreuzer *et al*[30]研究发现, NAD(P)H氧合酶在PDGF促HSC增殖过程中起重要作用, PDGF-BB通过激活NAD(P)H氧合酶而产生活性氧(ROS), ROS使p38 MAPK磷酸化而诱导HSC的增殖, 使用自由基清除剂MnTBAP(一种可通透细胞的SOD类似物)和NADPH氧化酶抑制剂二碘基苯均可抑制PDGF-BB诱导的细胞增殖效应, 并发现HSC可表达4种不同亚型的NAD(P)H氧合酶. Gabele *et al*[31]和Tsutsumi *et al*[32]证实了PDGF可通过S6激酶信号传导途径调节HSC的增殖和胶原基因的表达, p70S6K特异性抑制剂rapamycin可以抑制PDGF诱导的HSC增殖和I型胶原的表达, 但并不影响α-SMA的表达. Borkham-Kamphorst *et al*[33-34]构建了PDGF-β可溶性受体表达载体(sPDGFRb), 经尾静脉导入胆管结扎至肝纤维化动物模型后, 肝纤维化程度减轻, Ⅰ型胶原, α-SMA的表达下降. Di *et al*[35] 和Benedetti *et al*[36]研究发现, cariporide可以阻断PDGF促HSC增殖效应, 该药的作用机制是选择性的抑制Na^+/H^+交换器, 而不影响ERK1/2, Akt, PKC的激活, 同时, 把该药分别运用于二甲基亚硝酸及胆管结扎致肝纤维化的两种大鼠模型后, 能显著抑制HSC的活化, 增殖, 及胶原的分泌, 改善肝纤维化程度.

■创新盘点
本文就TGFβ、PDGF、瘦素、PPAR等受体的结构, 功能, 及目前干扰其信号途径的主要措施作了较全面的阐述.

1.3 瘦素(leptin)受体介导的信号转导途径 瘦素是ob基因编码的一种分泌蛋白质, 瘦素受体(LepR)由1165个氨基酸构成的一单次跨膜蛋白. 瘦素与受体结合后, 可影响机体许多生理系统和代谢途径, 具有广泛的生物学效应[37]. 最新的一些临床与基础研究显示, 瘦素与肝纤维化具有密切关系, 如促进Ⅰ型胶原[38], TGFβ, TIMP1等基因的表达, 作为新的肝纤维化的形成因子, 对其生物学作用和信号转导的研究已受到广泛的关注[39-42]. Ahima *et al*[43]研究表明, JAK STAT途径是瘦素的主要信号转导途径, 瘦素与受体结合后引起JAK1, JAK2及受体胞质区磷酸化, 进一步使下游胞质蛋白STAT磷酸化, STAT磷酸化后转入核内, 调控相应基因的表达. Saxena *et al*[44]发现, 使用JAK2激酶抑制剂AG490和受体磷酸化激酶抑制因子SOCS-3可以阻断瘦素的促HSC增殖效应, 同时发现瘦素增加ERK和Akt的磷酸化, 而对应激激活蛋白激酶和C-JUN氨基末端激酶磷酸化无明显影响, 使用PI3激酶抑制剂LY294002和ERK抑制剂PD98059也可以阻断瘦素的促HSC增殖效应, 提示瘦素使通过MAPK信号转导途径促进HSC的激活及胶原蛋白的表达. Cao *et al*[45]报道, 瘦素通过激活JNK1, JNK2而使H_2O_2表达增加, 再激活H_2O_2依赖的p38和ERK1/2途径而使HSC表达α1(Ⅰ)胶原增加. 使用ERK1/2抑制剂PD098059和P38抑制剂SB203580可以使HSC表达α1(Ⅰ)胶原下降. 越来越多的研究表明瘦素是一种多功能细胞因子, 目前瘦素促肝纤维化发生机制仍不明确, 阻断瘦素介导的信号转导途径有可能为肝纤维化的防治开辟一条新道路[46].

1.4 血管紧张素(AngⅡ)受体介导的信号转导途径 AngⅡ是肾素血管紧张素系统的主要生物活性肽, 目前许多研究表明, AngⅡ能促进HSC的激活, 增殖, 促使细胞外基质大量积聚, 在肝纤维化形成中起重要作用[47-48], AngⅡ是通过与细胞膜上特异性受体(ATR)结合而发挥作用的, AngⅡ受体主要有AT1R, AT2R二种亚型, HSC主要表达AT1R, ATR属G蛋白偶联受体, AngⅡ与受体结合后导致G蛋白活化, 活化的G蛋白可以激活下游效应分子, 如磷脂酶C(PLC), 磷脂酶A_2(PLA_2)等, 通过产生第二信使, 如cAMP、cGMP、DAG, IP3等调节相应基因的表达, 近年, 对AT1R介导的信号途径有了一些新的认识, Bataller *et al*[49]和Griendling *et al*[50]研究表明, AngⅡ与AT1R结合后, 激活NAD(P)H氧合酶诱导产生ROS, ROS再激活ERK-2, p38 MAPK, JNK等通路而调节HSC的增殖、迁移. Li *et al*[51]也发现, AngⅡ通过ERK1/2途径使AP-1活性增加, 促进α1(Ⅰ)型前胶原基因的表达. 因此, 血管紧张素转换酶抑制剂和血管紧张素1型受体拮抗剂有望成为防治肝纤维化的合适药物[52-54].

2 肝星状细胞激活与核受体信号转导途径

核受体是配体依赖性转录因子超家族, 与机体生长发育、细胞分化, 以及体内许多生理、代谢过程中的基因表达调控密切相关, 近年研究发现, PPAR, RXR, FXR等核受体介导的信号转导途径与肝星状细胞激活有密切关系.

2.1 过氧化物酶体增殖物激活受体(PPARs)介导的信号转导途径 过氧化物酶体增殖物激活受体, 属Ⅱ型核受体超家族, 包括PPAR-α, PPAR-β和PPAR-γ 3种类型, PPARs也是一种配体激活的转录因子, 与基因调控区的PPAR反应元件(PPRE)结合后调节相应基因的转录, 在脂代谢、糖代谢、细胞增殖分化等方面发挥重要作用, 近年发现, PPARs还可以影响HSC的激活及胶原的合成[55-56], Miyahara *et al*[57]发现, 胆管结扎致肝纤维化动物模型中, HSC中PPAR-γ mRNA表达下降近70%, 细胞核蛋白与PPRE结合力下降, 与NF-κb, AP-1结合却增加, 使用PPAR-γ特异性配体15dPGJ; (2)作用于HSC后可以抑制细胞增殖和α1(Ⅰ)前胶原的合成, PPAR-γ拮抗剂GW9662可以消除这种抑制作用. Hazra *et al*[58]构建了PPAR-γ重组腺病毒载体(AdPPAR-γ), 并将其转染到激活了的HSC后, 可以使消失的脂滴恢复, 其表型也从激活向静止转变, 同时也可抑制JunD与AP-1的结合、AP-1的活性. 同样Yavrom *et al*[59]使用AdPPAR-γ转染入HSC后, PPAR-γ表达上调导致α1(Ⅰ) mRNA下降约50%, 机制可能是抑制COL1A1启动子的活性, 且作用位点主要在启动子-133 bp区域, 免疫共沉淀分析, PPAR-γ通过抑制p300而阻滞NF-I蛋白和DNA结合. 这些研究表明, PPAR-γ是保持HSC静息状态所必需的, PPAR-γ配体有可能成为抗肝纤维化治疗一新的亮点[60-61].

2.2 视黄酸(RAR)和视黄醇(RXR)类核受体介导的信号转导途径 RAR和RXR属于类固醇和甲状腺激素受体超家族成员, 他们作为配体激活的转录因子, 结合到靶基因的特定应答序列(DNA)上, 如: 视黄酸应答元件(RARE), 再调节基因的转录表达. 受体由3

■同行评价
本文对肝星状细胞激活过程中的重要的膜受体信号途径、核受体信号转导途径及研究进展作了详细的阐述, 研究内容较全面, 并能突出进展, 具有一定的学术水平及指导价值.

种不同的基因: α, β和γ编码, 形成了RARα, RARβ, RARγ和RXRα, RXRβ, RXRγ等多种类型的受体. 考虑到HSC活化时伴有维生素A丢失, 预示恢复HSC内的维A酸水平是否可以抑制HSC的激活呢[62]? 研究发现, RAR, RXR特异性配体或把RARβ, RXRα表达质粒转染入PDGF刺激的大鼠肝星状细胞可抑制该细胞的增殖, 下调α-SMA的表达[63]. Hellemans *et al*[64]和Okuno *et al*[65]报道, 在HSC激活过程中RARα, β, γ, RXRα表达逐渐下降, 特别是RARα, β在新分离HSC的前3天下降显著, 同时发现RXRα转录子缺乏6, 7外显子, RXR激动剂AGN194204和RAR激动剂全反式维甲酸, 13-顺式维甲酸, 9-顺式维甲酸可以明显的抑制HSC的增殖, 而RAR激动剂TTNPB却无此效应, RXR激动剂AGN194204还具有抑制α1(Ⅰ)前胶原和纤维连接蛋白的合成. Wang *et al*[66]报道维甲酸作用于CCl_4所致的肝纤维化大鼠12 wk后, 治疗组肝组织中α2(Ⅰ)胶原和羟脯氨酸表达下降2-3倍, 作用机制可能与其抑制胶原纤维的表达、抗氧化等有关. Milliano *et al*[67]发现, 视黄醇、维甲酸可以抑制静息HSC的活化、增殖, 但并不能恢复细胞内的维生素A及RARα, β, γ, RXRα的水平, 也不能逆转已激活的HSC, 提示HSC激活后对细胞外视黄醇、维甲酸失去反应. 因此, RAR, RXR特异性配体抗肝纤维化作用还有待更深入研究.

2.3 法呢醇X受体(FXR)介导的信号转导途径 FXR激素核受体超家族成员, 具有典型的核受体结构, 在肝肠系统、肾、肾上腺均有FXR表达, 目前发现FXR具有α1, α2, β1, β2, 4种亚型, 在胆汁酸和脂质代谢中发挥重要作用, 6-ECDCA是FXR高亲和力特异性配体. Fiorucci *et al*[68-69]研究表明, FXR介导的信号途径与HSC活化及胶原的合成有密切关系, 使用6-ECDCA可以减轻猪血清和胆管结扎致肝纤维化动物模型肝纤维化程度, 下调肝星状细胞TGFβ, α-SMA,TIMP1的表达, 可能机制是6-ECDCA作用于FXR后诱导转录抑制因子SHP表达, SHP抑制AP-1结合DNA的活性. 另一研究发现, 6-ECDCA作用于FXR后, PPAR-γ表达升高达40倍, 提示FXR通过其与PPAR-γ之间的交叉串连而调节HSC的激活[70].

总之, 肝星状细胞激活过程中, 各种信号转导途径极为复杂, 一种细胞因子可以激活多条信号转导途径, 一条信号转导通路又可被多种细胞因子激活, 不同途径之间存在着多种交互联系, 形成错综复杂的信号调节网络. 近年关于HSC激活过程中的信号转导这方面的研究进展是日新月异, 干扰其主要的信号转导途径为肝纤维化治疗带来了新的曙光, 但是目前研究大多限于体外和动物实验, 且设计的信号转导干扰药物大多缺乏细胞特异性, 理想的抗肝纤维化药物应仅作用于肝脏, 特异性抑制细胞外基质合成或促进其降解, 而这正是我们今后研究的重点.

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