

# 肝星状细胞中的TGFβ信号转导通路

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## ■背景资料

肝星状细胞(HSC)活化是肝纤维化形成的中心环节, 转化生长因子β(TGFβ)启动了肝星状细胞的活化, TGFβ信号在HSC内主要通过ALK5/smad2/3途径在HSC内传递, 而近年来的研究表明, ALK1/smad1/5途径及非smad信号也起非常重要的作用. 有必要对HSC中复杂的TGFβ信号进行研究, 为有效抗TGFβ治疗肝纤维化提供新的思路.

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## Transforming growth factor β signaling in hepatic stellate cells

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## Abstract

The activation of hepatic stellate cells (HSCs) plays a central role in liver fibrogenesis. Transforming growth factor β (TGFβ) initiates the activation of HSCs. In HSCs, TGFβ signaling is mainly transduced through the ALK5/smad2/3 pathway. However, recent evidence has shown that the ALK1/smad1/5 pathway and non-Smad signaling also play important roles in the activation of HSCs. For determining an effective anti-TGFβ strategy for liver fibrosis, it is necessary to investigate the complex signaling of TGFβ in HSCs.

**Key Words:** Hepatic stellate cells; Transforming growth factor β; Signal transduction pathway

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## 摘要

肝星状细胞(hepatic stellate cell, HSC)活化是肝纤维化形成的中心环节, 转化生长因子β(transforming growth factor β, TGFβ)启动了肝星状细胞的活化, TGFβ信号在HSC内主

要通过ALK5/smad2/3途径在HSC内传递, 而近年来的研究表明, ALK1/smad1/5途径及非smad信号也起非常重要的作用. 有必要对HSC中复杂的TGFβ信号进行研究, 为有效抗TGFβ治疗肝纤维化提供依据.

**关键词:** 肝星状细胞; 转化生长因子β; 信号转导通路

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## 0 引言

HSC活化并分泌大量细胞外基质, 是肝纤维化形成的中心环节. TGFβ因启动、促进HSC活化而在肝纤维化形成过程中起重要作用. HSC中TGFβ信号主要通过ALK5/smad2/3途径传递, 而近年来的研究表明, ALK1/smad1/5途径及非smad信号也起非常重要的作用<sup>[1-2]</sup>.

## 1 HSC内Smad依赖的TGFβ信号通路

TGFβ超家族包括多种信号蛋白, 如TGFβ单体、骨形成蛋白(bone morphogenetic protein, BMP)、活化素(activin)等<sup>[3-4]</sup>, TGFβ通过其受体发挥作用<sup>[5-6]</sup>. TGFβ受体分3型: TβR I, TβR II, TβR III. 前两者为丝氨酸/苏氨酸受体, 配体与TβR II-TβR I结合形成异源性三聚体, TβR II激酶使TβR I磷酸化, 并激活TβR I激酶, 使特异性受体调节性Smads(regulation-smads, R-smads)磷酸化, 磷酸化的R-smads与通用Smads(common-partner-SMAD, CO-Smads)形成复合物转入核内参与靶基因的转录调节<sup>[7]</sup>.

TβR I 根据其激酶的不同又分为ALK1, ALK3, ALK5. TGFβ超家族信号可因配体及结合的受体不同分为两支<sup>[8-9]</sup>: 一支为TGFβ分支, 主要由TGFβ、活化素活化TβR I /ALK5受体, 激活Smad2, Smad3传导信号; 另一支为BMP分支, 主要由BMP、生长分化因子活化TβR I /ALK1受体, 激活Smad1, Smad5, Smad8向下游传递

信号. 在多数细胞类型, TGF $\beta$ 信号通过ALK5/Smad2/3传递. 既往认为ALK1特异性表达于内皮细胞, 最近的研究表明, HSC表面也有ALK1表达, 并通过第二支信号通路传递信号.

1.1 HSC内TGF $\beta$ /ALK5/Smad2/3途径及靶基因表达 TGF $\beta$ 可促进原代培养的HSC中Smad2的磷酸化、活化的HSC中Smad3磷酸化. 研究表明, Smad信号通路对TGF $\beta$ 介导的多种纤维性胶原基因的激活起关键作用, 包括COL1A1, COL1A2, COL3A1<sup>[10]</sup>等基因. 另有60多种ECM相关基因被认为是TGF $\beta$ 下游的即刻早期基因<sup>[11]</sup>, 如TIMP-1, PAI-1, b5整合素基因(INTB5)等.

Smad复合物进入细胞核内可直接与靶基因的启动子区反应元件相结合, 介导靶基因的上调<sup>[12]</sup>. Smad蛋白还可与其他转录因子相互作用, 促进或抑制基因的转录. Smad3与TFE3和Sp1相互作用, 分别活化PAI-1及COL1A2基因启动子<sup>[13-14]</sup>. 而Smad与AP-1的相互作用可加强<sup>[15-16]</sup>或减弱<sup>[17]</sup>基因的转录活性, 最终转录效应不仅取决于AP-1和/或Smad特异的cis元件, 还取决于两者的相对位置. 如果Smad特异序列远离功能性AP-1位点, 如PAI-1启动子, 则Smad靶基因转录活性增强, 且无需形成Smad/Jun二聚体. 相反, 如靶基因启动子的Smad特异反应元件内包含AP-1位点, Jun则通过结合、阻断Smad3的转录活化域, 直接抑制Smad功能<sup>[18]</sup>.

Smad还可通过与转录共刺激因子(如Ski相互作用蛋白或p300/CBP)相互作用而干扰其他转录因子的功能. Smad-p300/CBP相互作用对TGF $\beta$ 介导的胶原基因的转录激活是关键事件<sup>[19]</sup>. 干扰素- $\gamma$ 通过Jak-1诱导Stat1a, 后者与Smad3竞争p300/CBP, 从而抑制COL1A2基因的转录活性而发挥抗纤维化活性<sup>[20]</sup>.

TGF $\beta$ 除了调节细胞外基质(extracellular matrix, ECM)成分的基因表达, 尚可影响与ECM代谢密切相关的间质性胶原酶(matrix metalloproteinase-1, MMP-1)及其抑制因子(tissue inhibitors of metalloproteinases, TIMPs)的表达. Smad3, Smad4(而不是Smad1)的过度表达可与p300/CBP竞争, 从而阻断IL-1介导的MMP-1的转录激活<sup>[21]</sup>. TGF $\beta$ 促进TIMP-1、同时抑制MMP-1的表达, 两者都存在启动子附近AP1位点, 是TGF $\beta$ 发挥作用的关键, 但作用机制不尽相同. MMP-1启动子AP-1位点上游存在TGF $\beta$ 抑制元件<sup>[22]</sup>, Smad3可直接与AP-1位点相互作用介导TGF $\beta$ 对MMP-1基因表达的抑制. 而包含Smad的

复合物并不与TIMP-1的AP-1位点作用, Smad的过度表达未能促进TGF $\beta$ 对TIMP-1表达的诱导, TGF $\beta$ 作用于Smad2, Smad3或Smad4敲除的细胞系仍然可以诱导TIMP-1的表达, c-Fos, JunD, c-Jun则对TGF $\beta$ 诱导TIMP-1表达非常重要<sup>[23]</sup>.

Smad3在纤维化形成中具有重要作用, 其证据来自靶向敲除Smad3的小鼠的应用, 与野生鼠相比, Smad3敲除小鼠肝内I型胶原mRNA表达及羟脯氨酸含量明显减少<sup>[24]</sup>. 因此, 靶向Smad3的成为重要的抗纤维化治疗方向.

1.2 TGF $\beta$ /ALK1/Smad1途径 ALK1及下游通路被认为仅在内皮细胞中表达, 在内皮细胞中, TGF $\beta$ /ALK1通过Smad依赖方式上调分化抑制蛋白1(inhibitor of differentiation 1, Id1), 促进细胞的增殖和迁移. Wiercinska *et al*<sup>[25]</sup>在最近的研究中发现, HSC也可通过T $\beta$ R I /ALK1/Smad1通路传递信号. 为筛选与纤维化形成有关的TGF $\beta$ 靶基因, 他们分析了HSC中Smad7依赖的基因表达谱, 发现Smad7的表达可强烈抑制Id1的表达, Id1过度表达又通过抑制Smad7及 $\alpha$ -SMA纤维形成而促进HSC的活化, 反之, Id1敲除使 $\alpha$ -SMA纤维形成减少, 从而抑制HSC的活化, 因此认为Id1是致纤维化的一个重要因子. 进一步的研究发现, HSC表面也存在ALK1的表达, TGF $\beta$ 信号对Id1表达的影响是通过T $\beta$ R I /ALK1/Smad1通路传递, 而非T $\beta$ R I /ALK5/Smad2/3通路, 抑制Smad2/3活化可以抑制ECM基因的上调, 然而对 $\alpha$ -SMA表达没有作用. 对ALK5的抑制不能阻止Smad1的磷酸化, 因此, Smad1的磷酸化似乎对于 $\alpha$ -SMA的聚合不可或缺. BMP是ALK1受体的天然配体, 有研究表明, BMP-2, BMP-4作用于HSC, 促进 $\alpha$ -SMA的表达明显上升, 对于HSC的转化促进作用较TGF $\beta$ 1更强<sup>[26]</sup>, 有力的支持了ALK1信号通路在HSC的表达. 体内实验也表明, 纤维化的肝组织内Id1表达明显增多, 同时磷酸化的Smad1增多. 在HSC活化过程中, Smad1表达的增加和磷酸化以往曾有报道<sup>[27]</sup>, 提示TGF $\beta$ /ALK1/Smad1依赖途径在肝纤维化的发生中可能起重要作用.

1.3 HSC中2种信号表达的意义 在内皮细胞中, 上述信号分别介导2种不同的效应, ALK1/Smad1/5的活化导致内皮细胞迁移和增殖, ALK5/Smad2/Smad3信号作用则相反<sup>[28-29]</sup>. 内皮细胞的最终活化状态依赖于2种信号的平衡. 同样, HSC和活化的HSC(MFB)接受TGF $\beta$ 刺激后也表现出不同的细胞内反应<sup>[30]</sup>, 主要表现在以

#### ■ 相关报道

既往研究对TGF $\beta$ 信号传导通路中ALK5/sm2/3途径在肝纤维化的形成中的意义及Smad蛋白对基因转录的调控机制已有了较为深入的了解, 但对HSC中ALK1/sm1/5途径的研究及报道较少, 此途径在内皮细胞的研究中较多, 最近有学者开始对此途径在HSC中的传递进行了探索性的研究(参见参考文献[25-26,47]), 并发现其在肝纤维化的形成中具有重要作用.

## ■应用要点

TGF $\beta$ 可能通过多种信号转导途径促进肝纤维化的进展,对信号转导途径的深入研究可为有效抗TGF $\beta$ 治疗肝纤维化提供新的思路。

下几方面。

1.3.1 细胞生长受抑制情况不同 研究表明新分离静止的HSC在TGF $\beta$ 1作用后其增殖受到抑制,而活化的HSC则表现为增殖、收缩能力显著加强<sup>[31-32]</sup>。但均出现多种细胞外基质成分显著上调<sup>[33]</sup>。

1.3.2 TGF $\beta$ 受体表达情况 静止的HSC不表达T $\beta$ R I及T $\beta$ R II受体,或表达极微弱。培养活化后,受体mRNA及蛋白表达明显上升,但受体与配体亲和力明显下降,同时Smad4复合物与DNA的亲和力下降<sup>[34]</sup>。

1.3.3 TGF $\beta$ 下游信号传导情况 原代HSC接受内源性或外源性TGF $\beta$ 刺激后,最主要的细胞内信号蛋白改变在于Smad2, Smad3的磷酸化和抑制性Smad7的表达。静止的HSC极少见到Smad2磷酸化,活化后HSC中Smad2则出现明显磷酸化,且随着Smad2的高度磷酸化,Smad7表达显著升高<sup>[35]</sup>。而慢性肝损伤过程中,HSC呈现持续活化( $\alpha$ -SMA持续表达),Smad2磷酸化组成性表达,但Smad7表达持续在一较低水平。

静止的HSC受到TGF $\beta$ 处理,可出现Smad2和Smad3的磷酸化和核转位。活化的HSC接受TGF $\beta$ 处理后,没有出现磷酸化Smad2, Smad3的显著增加,提示MFB失去了对TGF $\beta$ 的敏感性<sup>[36]</sup>。

由于目前对HSC中ALK1/Smad1/5途径研究较少,上述不同是否与此有关尚需进一步证实,但为下一步研究提供了重要方向。

1.4 辅助性TGF $\beta$ 受体对不同信号途径的调节作用 TGF $\beta$ III型受体包括 $\beta$ 聚糖和endoglin,在TGF $\beta$ 信号转导中起间接作用。二者结构相似,都是跨膜受体,细胞内结构域较短,缺少酶作用基序,但包含许多丝氨酸、苏氨酸残基。 $\beta$ 聚糖的重要作用是促进TGF $\beta$ 2与T $\beta$ R II的结合。辅助受体endoglin仅与结合在T $\beta$ R II上的配体相结合,由于T $\beta$ R II与TGF $\beta$ 1和TGF $\beta$ 3比TGF $\beta$ 2具有更高的亲和力,endoglin与此二者作用更有效<sup>[37-38]</sup>。近年研究认为,endoglin在调节TGF $\beta$ /ALK1和TGF $\beta$ /ALK5信号通路过程中起重要作用。

Endoglin的胞外段与胞内段均可与T $\beta$ R II和ALK5相互作用,其胞内域富含丝氨酸、苏氨酸残基,可为ALK5及T $\beta$ R II磷酸化<sup>[39]</sup>。外源性表达endoglin能下调TGF $\beta$ 诱导的单核细胞及成肌细胞生长抑制<sup>[40]</sup>,还可抑制TGF $\beta$ 诱导的成肌细胞外基质的合成<sup>[41]</sup>。应用反义寡核苷酸或endoglin中和抗体作用于内皮细胞,可以加强TGF $\beta$ 对内皮细胞迁移、生长的抑制作用<sup>[42-43]</sup>,

而这些作用是由ALK5介导的<sup>[44]</sup>,因此,可以认为endoglin是TGF $\beta$ /ALK5信号通路的负性调节因子。与此相一致,外源性表达endoglin可以抑制Smad3的转录活性<sup>[45]</sup>。

由于ALK1或endoglin的变异均可导致遗传性出血性毛细血管扩张症,因此可能两者具有共同的信号通路。最近的研究认为,endoglin是ALK1磷酸化的底物,TGF $\beta$ /ALK1信号需要endoglin。并且,endoglin表达水平决定了内皮细胞的生长能力。缺乏endoglin的情况下,ALK1信号减弱同时ALK5信号增强,内皮细胞生长受抑。Endoglin可能作为TGF $\beta$ /ALK1和TGF $\beta$ /ALK5之间平衡的一个调节因子。目前的研究结果支持这样的模型: endoglin刺激TGF $\beta$ /ALK1信号同时间接抑制TGF $\beta$ /ALK5信号,从而促进血管生成相的活化<sup>[46]</sup>。

HSC中存在2种TGF $\beta$ 信号通路,其调控机制尚不清楚。最近研究表明HSC表面同样存在endoglin的表达<sup>[47]</sup>,且在转化的HSC中,endoglin的表达水平增高。是否endoglin通过与内皮细胞类似的调节方式调节肝HSC的致纤维化反应仍需进一步研究。

## 2 TGF $\beta$ 的非Smad通路

除了TGF $\beta$ /Smad通路,TGF $\beta$ 还可活化其他的信号级联反应<sup>[48]</sup>。TGF $\beta$ 能活化Erk, JNK及p38 MAPK激酶通路,并可能独立于Smad而发挥作用<sup>[49]</sup>,如活化NF- $\kappa$ B导致生物学效应。Erk, JNK途经的激活还可导致并调节Smad的磷酸化<sup>[50]</sup>,将MAPK与Smad信号联系起来。TGF $\beta$ 诱导的Ras/Erk MAPK信号能诱导TGF $\beta$ 1的表达,从而扩大TGF $\beta$ 的反应<sup>[51]</sup>。TGF $\beta$ 依赖的p38MAPK途径可以上调HSC细胞外基质的表达<sup>[52]</sup>,如I型胶原和凝血酶敏感素-2(TSP-2)。

TGF $\beta$ 诱导MAPK通路活化,也可能直接影响Smad相互作用转录因子,如JNK底物c-Jun或p38MAPK底物活化转录因子2(activating transcription factor 2, ATF-2),从而将Smad通路与MAPK通路联系起来<sup>[5]</sup>。两条通路既相互促进,又相互拮抗。TGF $\beta$ 活化Smad和MAPK通路的双重能力对TGF $\beta$ 诱导的上皮细胞向间质细胞的转化起重要作用<sup>[53]</sup>; c-Jun可通过Smad共抑制因子相互作用抑制Smad2的信号通路,这种作用是通过JNK信号调节,而Smad7可加强和维持JNK的活化<sup>[54]</sup>,因此,Smad与MAPK通路之间活化平衡可能最终决定细胞对TGF $\beta$ 信号的反应。

由于TGF $\beta$ 在肝纤维化进展中的重要作用, 抗TGF $\beta$ 治疗方兴未艾. 然而, TGF $\beta$ 在体内作用广泛, 需要更深入了解其复杂的信号传导通路及相互之间的关系, 为寻找有效治疗肝纤维化的方法提供理论依据.

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### ■同行评价

本文就肝星状细胞中的TGF $\beta$ 信号转导通路进行了文献回顾, 选题较新颖, 行文流畅, 从一个侧面详细概述了肝星状细胞与TGF $\beta$ 的关系, 有一定的学术价值.

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