

# C/EBP $\alpha$ 基因与PARs在肝星状细胞激活中的作用及关系

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## ■背景资料

肝纤维化是严重威胁人类健康的重要疾病之一,迄今没有理想的治疗方法。研究表明肝星状细胞的激活是肝纤维化的关键,如何抑制肝星状细胞的激活,诱导其凋亡是目前肝纤维化研究的重点。

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## Roles and relation between C/EBP $\alpha$ and PARs in the activation of hepatic stellate cells

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## Abstract

Protease activated receptors (PARs) are main components of the fibrotic cascade mediated by the trypsin and thrombin that amplifies liver inflammation and fibrosis. Gene transcription initiation induced by PARs plays an important role in the activation of hepatic stellate cells (HSCs). HSC activation can be inhibited by the expression of transcription factor CCAAT enhancer binding proteins  $\alpha$  (C/EBP $\alpha$ ). Further research of the relation between C/EBP $\alpha$  and PARs will contribute to the understanding of the pathogenesis of liver fibrosis and provide a theoretical basis for further exploration of anti-fibrotic strategies.

Key Words: CCAAT enhancer-binding protein  $\alpha$ ; Protease-activated receptors; Liver fibrosis; Hepatic stellate cells

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## 摘要

蛋白酶活化受体家族(protease activated receptors, PARs)可通过MAPK/ERK信号通路激活细胞内部分转录因子,从而参与肝纤维化的形成,是肝纤维化自动放大循环过程中主要炎症和纤维化受体。肝星状细胞(hepatic stellate cells, HSC)的活化是肝纤维化的关键, HSC活化的显著变化是细胞内维生素A和脂滴的减少和消失,而转录因子CCAAT增强子结合蛋白 $\alpha$ (C/EBP $\alpha$ )在维持脂肪细胞分化中起着重要作用,因此其对肝纤维化形成过程中肝星状细胞的活化具有负性调控作用,上调其表达可以抑制肝星状细胞增殖和活化,并诱导肝星状细胞的凋亡。深入研究PARs与C/EBP $\alpha$ 的关系,将有助于对肝纤维化发生机制的理解,从而为抗肝纤维化治疗提供新的理论依据。

关键词: CCAAT增强子结合蛋白 $\alpha$ ; 蛋白酶活化受体家族; 肝纤维化; 肝星状细胞

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## 0 引言

肝星状细胞(hepatic stellate cells, HSC)在组织炎症坏死区域由静止的贮存维生素A表型向活化的肌成纤维细胞转化并分泌细胞外基质(extracellular matrix, ECM)的过程是肝纤维化的中心环节<sup>[1-4]</sup>。蛋白酶活化受体家族(protease activated receptors, PARs)是凝血酶和胰蛋白酶介导的肝纤维化自动放大循环过程中主要的炎症和纤维化受体, HSC活化过程中, PARs介导的基因转录启动起着重要作用<sup>[5-7]</sup>。已有研究证实转录因子CCAAT增强子结合蛋白 $\alpha$ (CCAAT enhancer binding proteins  $\alpha$ , C/EBP $\alpha$ )的表达可以抑制HSC的活化、维持其静止状态<sup>[8-11]</sup>。本文就HSC、C/EBP $\alpha$ 对PARs激活HSC促肝纤维化形成的影

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响等方面作一综述, 为进一步研究抗肝纤维化治疗打下基础。

## 1 形成肝纤维化的细胞学基础

肝纤维化的本质是以胶原为主要成分的ECM合成和分泌增多, 降解相对减少, ECM过度沉积。ECM主要由I、III型胶原构成, 其中I型胶原是其主要成分<sup>[1,11-13]</sup>。因此胶原蛋白的来源一直都是肝纤维化研究的重点。Ikegami等<sup>[14,15]</sup>研究表明肝细胞和胆管上皮细胞的上皮-间质转型可以作为其来源之一; Forbes等<sup>[16-18]</sup>证明骨髓来源的肌成纤维细胞也参与了肝纤维化中胶原蛋白的合成; 循环中的单核细胞亚群进入受损的肝组织后也可以向纤维细胞分化<sup>[19,20]</sup>; 但是目前Friedman等<sup>[21-23]</sup>研究一致认为HSC是正常及纤维化肝脏中产生ECM的主要细胞。

HSC最初由Kuffer等<sup>[24,25]</sup>在1876年发现并命名为“星状细胞”, 直到1996年国际上才统一命名为肝星状细胞。生理情况下HSC约占肝内细胞总数的5%-8%, 主要位于肝索与肝窦壁之间的Disse间隙内, 主要功能为贮存维生素A(约贮存人体80%的维生素A)和脂肪<sup>[26,27]</sup>, 合成少量的ECM, 主要以IV型胶原为主。在肝脏损伤过程中, 静止的贮存维生素A和脂滴的HSC经过一系列表型转化向活化的缺乏维生素A和脂滴的肌成纤维细胞转变, 从而合成和分泌大量的ECM<sup>[28,29]</sup>。 $\alpha$ -平滑肌肌动蛋白( $\alpha$ -smooth muscle actin,  $\alpha$ -SMA)被认为是HSC激活的标志性蛋白, 合成和分泌I、III型胶原被认为是HSC活化的特征<sup>[30-32]</sup>。HSC的激活可以分为3个阶段: (1)前炎症阶段: 各种损伤因素损伤肝细胞, 致使肝细胞分泌多种丝裂原样物质, 始动激活HSC转化为肌成纤维细胞(Myofibroblasts, MFB)(直接旁分泌通路); (2)炎症阶段: 肝细胞损伤, 活化肝内的巨噬细胞和血小板分泌大量的炎性介质, 进一步促进HSC激活为MFB(旁分泌活化通路); (3)炎症后阶段: 激活的HSC及MFB自身分泌一些炎性因子(自分泌活化通路), 使肝纤维化的过程即使在去除肝损伤因素后也得以持续<sup>[33-35]</sup>。因此HSC的激活是肝纤维化的关键, 抑制HSC的激活对于肝纤维化的防治至关重要。

## 2 PARs及其在肝星状细胞激活中的作用

PARs属于G-蛋白偶联受体家族。通过分子克隆技术发现的PARs成员共有4个(PAR1-4), 其中PAR1、PAR3是凝血酶受体, PAR2为胰蛋白酶

受体, PAR4既可被凝血酶活化又可被胰蛋白酶活化, PAR3是PAR4的一个辅因子, 两者在活性上无明显差异<sup>[36,37]</sup>。人体内几乎所有细胞均有不同类型的PARs的存在与表达, 其能调节细胞增殖、分化等而参与多种生理和病理过程<sup>[38-40]</sup>。

研究表明: 无论是在急性还是慢性肝脏疾病中均可发现凝血酶和胰蛋白酶受体PARs的表达, 且随着肝脏受损程度的加重, 其表达含量逐渐升高<sup>[41]</sup>。Fiorucci等<sup>[38]</sup>研究证明: PARs家族的所有成员均可参与大鼠HSCs的激活和增殖。顾小红等<sup>[42,43]</sup>研究也证实: 无论是肝纤维化大鼠肝组织还是正常大鼠肝脏分离和培养的HSC均表达PAR1、2, 且与HSC激活的标志性蛋白 $\alpha$ -SMA的表达呈一致性, 说明PARs是肝纤维化自动放大循环过程中的主要炎症和纤维化受体。研究PARs如何将细胞外信号传递到细胞内引起细胞核反应发现, PARs可以通过胞外信号调节激酶(extracellular signal-regulated kinase, ERK)/丝裂原活化蛋白激酶(mitogen-activated protein kinase, MAPK)信号通路将细胞外信号传递到细胞内引起细胞核反应从而使许多转录因子的某些氨基酸残基磷酸化而活化, 启动细胞的增殖和分化<sup>[44-46]</sup>。

## 3 C/EBP $\alpha$ 蛋白在肝星状细胞激活中的作用

关于HSC如何被激活的机制研究很多<sup>[47-49]</sup>, 基因转录水平的调控几乎参与了真核细胞所有蛋白及因子的表达, 上百种不同转录因子参与了HSC由静止到激活过程的转变, 包括CCAAT增强子结合蛋白质超家族(C/EBPs)<sup>[50,51]</sup>。C/EBPs属于bZIP(basic region/leucine zipper)DNA结合蛋白超家族, 主要在小肠、肺脏、肾上腺、胎盘, 尤其在肝脏和脂肪组织等脂类和胆固醇相关复合物代谢旺盛的组织中优先表达, 而在脑、肾、胸腺、睾丸和卵巢中表达含量非常低<sup>[52,53]</sup>。C/EBPs可以结合并转录激活特定基因DNA增强子5'-RTTGCGYAAAY-3'(R = A或G, Y = C或T)重复序列或其变异体, 对基因的转录进行正负调控, 在细胞增殖、分化等过程中起重要的作用<sup>[9,54,55]</sup>。

C/EBPs蛋白超家族最初被研究在脂肪细胞的转录调控中起重要的作用<sup>[9,11,56]</sup>。肥胖的基因研究表明: 在脂肪细胞生成过程中, C/EBPs按一定的时序表达, 且每个成员都参与其特定的调控作用, 其中C/EBP $\alpha$ 的主要功能是促进脂肪细胞进入终末分化<sup>[56,57]</sup>。研究基因敲除动物模型结

### ■研究前沿

蛋白酶活化受体(PARs)可以通过激活细胞内的部分转录因子而介导肝星状细胞的增殖和活化, 肝星状细胞活化的显著特点是细胞内脂滴和维生素A减少甚至消失, 而转录因子CCAAT增强子结合蛋白可以维持脂肪细胞的分化, 进而维持肝星状细胞处于静止状态。深入研究PARs与CCAAT增强子结合蛋白的关系将有助于更好的理解肝纤维化的机制。

## ■相关报道

对于CCAAT增强子结合蛋白如何维持肝星状细胞的静止, 诱导其凋亡, Wang等研究表明其可以通过PPAR $\gamma$ 上调p53基因从而诱导HSC的凋亡。

构显示: 将C/EBP $\beta$ 基因导入C/EBP $\alpha$ -/-小鼠内, 肝内所表达的C/EBP $\beta$ 蛋白可以取代C/EBP $\alpha$ 蛋白发挥相应的作用, 但脂肪组织的形成有障碍, 说明C/EBP $\alpha$ 基因单独表达足以诱导前脂肪细胞3T3-L1向脂肪细胞分化<sup>[58]</sup>。Mauser等<sup>[59,60]</sup>研究表明, C/EBP $\alpha$ 过表达可以加速前脂肪细胞向成熟细胞的分化, 而反义C/EBP $\alpha$ RNA的表达则可以阻止前脂肪细胞的分化过程, C/EBP $\alpha$ 基因纯和缺失的动物中白色和棕色脂肪均减少, 这些研究均表明C/EBP $\alpha$ 在维持脂肪细胞分化成熟中起着重要的作用。

鉴于C/EBP $\alpha$ 转录因子与维持脂肪细胞分化的相关性和HSC激活过程中维生素A和脂滴的消失现象, 许多学者开始致力于HSC激活过程中C/EBP $\alpha$ 的表达情况及其与HSC激活、增殖关系的研究。结果发现: 静止的HSC中有C/EBP $\alpha$ ,  $\beta$ 和 $\delta$ 的表达, 活化的HSC及纤维化的肝脏中C/EBP $\alpha$ 的表达下降<sup>[61-63]</sup>。体外研究发现在活化的HSC中上调C/EBP $\alpha$ 基因可以抑制HSC的增殖、ECM的产生及 $\alpha$ -SMA的表达, 进而诱导脂滴的重新形成<sup>[64,65]</sup>。体内研究也证实了这一点, CCL4诱导小鼠慢性肝纤维化形成12 wk的模型中, 干预的最初1-4 wk和最后9-12 wk均可测得C/EBP $\alpha$ 的高表达, C/EBP $\alpha$ 的高表达明显降低胶原蛋白及羟脯氨酸的表达<sup>[58-66]</sup>。因此, C/EBP $\alpha$ 在受损的肝脏中对HSC的激活可能存在负性调控作用。但目前对于C/EBP $\alpha$ 如何影响HSC的机制尚未完全阐明。黄光存等<sup>[8]</sup>研究表明: 过表达C/EBP $\alpha$ 可以通过PPAR $\gamma$ 上调p53基因的表达, 进而上调Fas、肿瘤坏死相关因子凋亡诱导配体及DR5的表达, 从而诱导HSC的凋亡, 抑制肝纤维化。

## 4 结论

紧扣PARs可通过激活MAPK/ERK信号级联将细胞外信号传递到细胞内引起细胞核反应使许多转录因子活化, 进而介导肝纤维化自动放大循环过程, 受到C/EBP $\alpha$ 转录因子抑制HSC活化和增殖的启发, 我们认为: PARs通过MAPK/ERK信号通路将细胞外信号传递到细胞内, 引起细胞核反应, 使许多转录因子活化, 但C/EBP $\alpha$ 活化促使脂肪细胞分化维持HSC的静止作用难以抗衡PARs对HSC的激活作用, 如果采用外源C/EBP $\alpha$ 来增强细胞内C/EBP $\alpha$ 的表达, 并将其引入到PARs激活HSC中, 深入研究C/EBP $\alpha$ 与PARs在HSC激活中的相互关系, 以期能进一步了解HSC激活机制, 为临床肝纤维化防治寻求新靶点。

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# 创新盘点

本文结合肝星状细胞激活的内外机制, 将蛋白酶活化受体与转录因子CCAAT增强子结合蛋白引入到激活的肝星状细胞中, 以期发现肝星状细胞激活的机制提供新的依据。

## ■同行评价

本文从细胞水平阐述了肝星状细胞在肝纤维化过程中的可能作用机制,从基因、蛋白水平推测了C/EBP $\alpha$ 基因与PARs在上述过程中的表达变化及作用,并提出了自己的观点及可能的研究方向,为肝纤维化的防治提供靶点。

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## • 消息 •

## 《世界华人消化杂志》参考文献要求

**本刊讯** 本刊采用“顺序编码制”的著录方法,即以文中出现顺序用阿拉伯数字编号排序。提倡对国内同行近年已发表的相关研究论文给予充分的反映,并在文内引用处右上角加方括号注明角码。文中如列作者姓名,则需在“Pang等”的右上角注角码;若正文中仅引用某文献中的论述,则在该论述的句末右上角注角码。如马连生<sup>[1]</sup>报告……,潘伯荣等<sup>[2-5]</sup>认为……;PCR方法敏感性高<sup>[6-7]</sup>。文献序号作正文叙述时,用与正文同号的数字并排,如本实验方法见文献[8]。所引参考文献必须以近2-3年SCIE, PubMed,《中国科技论文统计源期刊》和《中文核心期刊要目总览》收录的学术类期刊为准,通常应只引用与其观点或数据密切相关的国内外期刊中的最新文献,包括世界华人消化杂志(<http://www.wjgnet.com/1009-3079/index.jsp>)和 *World Journal of Gastroenterology* (<http://www.wjgnet.com/1007-9327/index.jsp>)。期刊:序号,作者(列出全体作者),文题,刊名,年,卷,起页-止页, PMID编号;书籍:序号,作者(列出全部),书名,卷次,版次,出版地,出版社,年,起页-止页。