

# NDRG2与肝纤维化相关性的研究进展

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## NDRG2 and hepatic fibrosis

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## Abstract

N-mycdown stream-regulated gene 2 (NDRG2) is a potential regulator of liver fibrosis. Enhanced NDRG2 expression inhibits hepatic stellate cell activation, promotes the degradation of extracellular matrix, and regulates the regeneration of the liver. In addition, NDRG2 contributes to an enhanced capacity of liver and other tissues to hypoxic stresses. This article reviews the relationship between NDRG2 expression and liver fibrosis.

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Key Words: N-mycdown stream regulated gene; Hepatic fibrosis; Hepatic stellate cells; Hypoxia inducible factor-1

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## 摘要

NDRG2(N-mycdown stream regulated gene)基因是多种癌症的候选抑癌基因,并在肝纤维化的发生发展中扮演重要角色,通过抑制肝星形细胞激活、促进细胞外基质降解、调节肝细胞再生、增强肝细胞缺氧应激能力等多种途径调节肝纤维化进程. 本文就NDRG2与肝纤维化的关系作一综述.

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关键词: NDRG2; 肝纤维化; 肝星形细胞; 缺氧诱导因子

核心提示: 本文就NDRG(N-mycdown stream regulated gene)基因对肝星形细胞(hepatic stellate cell, HSC)激活、肝细胞外基质降解、肝细胞再生、肝细胞缺氧应激损伤等几方面,探讨NDRG2基因影响肝纤维化的机制.

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## 0 引言

NDRG(N-mycdown stream regulated gene)是近年来新发现的基因,因受N-Myc的抑制而得名. NDRG家族在人和鼠之间保持较高的同源性,人和鼠NDRG2基因同源性为92%<sup>[1]</sup>. 现已克隆的人源NDRG基因包括NDRG1、NDRG2、NDRG3和NDRG4, NDRG2于1999年首次被成功克隆<sup>[2-4]</sup>. 研究表明, NDRG2基因为多种癌症的候选抑癌基因<sup>[5-8]</sup>,在心、脑、肺、肝、骨骼肌等多种组织器官均有表达<sup>[9,10]</sup>. NDRG2与肝纤维化<sup>[11]</sup>及肿瘤的发生、发展与转归<sup>[12]</sup>、缺氧应激<sup>[13]</sup>、缺血再灌注损伤<sup>[14]</sup>、组织胚胎的发育和细胞的分化<sup>[15]</sup>等密切相关. NDRG2可通过多种途径调控肝脏的生理病理过程,在肝纤维化的发生发展中, NDRG2亦可能扮演重要角色,现介绍如下.

## ■背景资料

NDRG2基因是一种抑癌基因,并与肝纤维化密切相关,通过多种途径参与肝纤维化进程,并且该基因的表达水平与肝纤维化的进展存在相关性.

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## ■ 研发前沿

*NDRG2*基因是近年新发现的与肝纤维密切相关的基因,其影响肝纤维的机制仍有待深入研究,该基因在慢性肝损伤-肝纤维-肝硬化的发展病程中的表达,是否存在规律性也有待进一步研究。

## 1 抑制肝星形细胞的活化

肝星形细胞活化是肝纤维化形成的重要环节<sup>[16,17]</sup>,生理情况下肝星形细胞(hepatic stellate cell, HSC)处于静止状态,在各种肝损伤因素刺激下HSC被激活<sup>[18]</sup>, $\alpha$ -平滑肌肌动蛋白( $\alpha$ -smooth muscle actin,  $\alpha$ -SMA)是肝星形细胞活化标志物,转化生长因子- $\beta$ 1(transforming growth factor- $\beta$ 1, TGF- $\beta$ 1)是HSCs激活和胶原生成经典的激动因子<sup>[19,20]</sup>。TGF- $\beta$ 1/Smad信号转导通路与肝纤维化密切相关,其通过介导HSCs活化、增加细胞外基质(extracellular matrix, ECM)沉积、调节肝细胞生长等途径,参与肝纤维化的形成<sup>[21-23]</sup>。将洗脱血清后的LX-2细胞(肝星形细胞),用TGF- $\beta$ 1处理24 h,与对照组相比,处理组 $\alpha$ -SMA表达水平升高,NDRG2表达受到抑制,提示TGF- $\beta$ 1能促进LX-2活化。经腺病毒诱导NDRG2过表达,能够降低基础条件下LX-2细胞活化引起的 $\alpha$ -SMA蛋白表达水平,亦能降低经TGF- $\beta$ 1诱导引起的 $\alpha$ -SMA蛋白表达水平。 $\alpha$ -SMA表达增加时,NDRG2 mRNA和蛋白表达水平均降低。HSCs激活能够诱导NDRG2 mRNA和蛋白表达水平均降低,而增强NDRG2表达则能够减少Smad转录及磷酸化,通过阻断TGF- $\beta$ 1/Smad信号通路,抑制HSCs活化。同时也发现,NDRG2抑制HSCs活化不受TGF- $\beta$ 1的影响,并且增加HSCs MMP的表达<sup>[11]</sup>。

## 2 调控肝细胞外基质降解

肝纤维化的发生是细胞外基质沉积过多和/或降解减少的结果<sup>[24]</sup>,生理情况下,基质金属蛋白酶(matrix metalloproteinase, MMP)促进细胞外基质的降解,基质金属蛋白酶抑制蛋白(tissue inhibitors of metalloproteinase, TIMP)抑制细胞外基质的降解,二者之间分泌失衡是导致多种组织纤维化的重要因素之一<sup>[25-27]</sup>。在肝纤维化过程中,MMP2/TIMP2比例决定了细胞外基质的沉积与否以及肝纤维化的形成<sup>[28,29]</sup>。研究表明,TGF- $\beta$ 1诱导的LX-2细胞活化能增加MMP2、TIMP2的表达水平,与 $\beta$ -半乳糖苷酶组比较,经腺病毒诱导NDRG2过表达通过抑制TGF- $\beta$ 1/Smad信号通路升高MMP2水平,同时降低TIMP2水平,升高MMP2/TIMP2比例,从而减少二甲基亚硝胺(Dimethylnitrosamine, DMN)肝纤维化模型大鼠肝细胞外基质的沉积<sup>[11]</sup>。上述研究结果与Takahara等<sup>[30]</sup>在DMN肝纤维化模型中的认识相一致,即“随着纤维化的进展,肝细胞NDRG2基因表

达下调”。在肿瘤的发生发展过程中,MMP2通过降解肿瘤细胞外基质,促进肿瘤的转移、侵袭。有研究表明在肝细胞癌中,NDRG2通过抑制MMP2的表达降低肿瘤细胞对周围组织的侵袭力<sup>[31]</sup>。另一项研究认为,NDRG2通过下调MMP2水平影响肝癌细胞株的增殖能力和拮抗TGF- $\beta$ 1介导的肝癌细胞侵袭<sup>[32]</sup>。这与NDRG2在肝纤维化发展过程中对MMP2的调节并不一致,但其内在机制尚不清楚。

## 3 调控肝细胞生长

NDRG2 mRNA和蛋白在不同胚胎发育期的人和 大鼠肝组织中的表达水平存在差异,通常在胚胎发育早期较低,后期则明显升高<sup>[33,34]</sup>。NDRG2参与肝细胞的再生、分化、信号转导等生理过程,当肝脏再生能力达到一定峰值时,NDRG2 mRNA和蛋白表达水平显著降低。经腺病毒转染诱导肝细胞NDRG2高表达,通过诱导p53和p21调节Bax/Bcl-2升高,同时抑制cyclin E-Cdk2表达,致使细胞周期静止,从而发挥抗增殖作用,与对照组相比细胞凋亡比例由9.4%升高至64.7%<sup>[35]</sup>。在DMN肝纤维化模型中,诱导NDRG2高表达能够促进肝细胞再生、改善肝脏功能,并不引起肝细胞凋亡<sup>[11]</sup>。NDRG2 mRNA和蛋白在鼠和人胚胎肝脏中高表达,且其表达水平随着肝脏的发育而逐渐升高<sup>[34]</sup>,而在部分肝切除模型肝再生过程中其表达呈现先下降后上升的趋势,即NDRG2蛋白和mRNA水平在肝细胞进入增殖阶段时(48 h内)表达下调,在肝细胞进入分化阶段时(48 h后)表达上调。NDRG2高表达导致肝细胞周期阻滞于G<sub>1</sub>/S期,表达下调则促进肝细胞周期G<sub>1</sub>/S期转换的顺利进行。NDRG2通过上调p21,抑制cyclin E实现对肝再生时肝细胞周期的调控<sup>[36,37]</sup>。

## 4 抗缺氧应激损伤

缺氧能够诱发基因和蛋白质组学的改变<sup>[38]</sup>,导致细胞周期终止、分化、凋亡、坏死<sup>[39,40]</sup>。低氧通过影响成纤维细胞的活性、胶原的合成与降解及生长因子的分泌,参与病理性瘢痕的形成<sup>[41]</sup>。病理性瘢痕组织中HIF-1 $\alpha$  mRNA及蛋白质表达水平均明显高于正常皮肤组织<sup>[42]</sup>。肝纤维化发生时,肝细胞外基质过度沉积,肝细胞缺血缺氧,缺氧诱导因子在肝纤维发生发展中扮演重要角色<sup>[43,44]</sup>。NDRG2是HIF-1的下游目的基因,参与HIF-1基因介导的多种缺氧应答反应。快速生长的肿瘤组织伴随癌细胞微环境的变化,因为

肿瘤细胞的快速分化, 导致局部血管无法提供充分的氧气和营养<sup>[45]</sup>. 缺氧成为实体瘤的病理特征之一<sup>[46]</sup>. 研究发现, 将人类肺癌细胞株A549细胞暴露在缺氧(2%O<sub>2</sub>)或类似的环境中, 能够明显增强NDRG2 mRNA的表达. 用干扰RNA(siRNA)阻断A549细胞内源性HIF-1 $\alpha$ 表达, 缺氧诱导NDRG2高表达现象便消失. 缺氧通过HIF- $\alpha$ 1, 促进NDRG2基因表达增加. NDRG2增强A549细胞对缺氧诱导凋亡的敏感性, 促进肿瘤细胞的凋亡. 阻断HIF-1 $\alpha$ 表达或敲除HRE1只能减少约60%或80%的缺氧应答反应, 表明还有其他因素参与缺氧诱导的NDRG2上调, 如p53、核因子 $\kappa$ B(nuclear factor kappa B, NF- $\kappa$ B)、SP1等NDRG2的上游基因<sup>[47]</sup>. 实体瘤“缺氧”特征与肝纤维化、肝硬化细胞外基质过度沉积、假小叶形成、血管重建等所致的“缺氧”存在相似性, HIF- $\alpha$ 1的激活促进NDRG2基因的表达, 因此NDRG2在抗肝纤维化缺氧应激损伤方面可能发挥积极作用.

## 5 讨论

肝纤维化是慢性肝病向肝硬化、肝癌发展的过渡阶段, 其发展转归可对疾病预后产生重要影响. 目前的观点认为, 慢性肝损伤-肝纤维化-肝硬化-肝癌是慢性肝病由轻到重的一般进展模式. 肝纤维化的基本病理特征为肝细胞外基质的过度沉积, 其病理环节涉及HSCs的激活<sup>[18]</sup>、MMP/TIMP比例的失衡<sup>[25-27]</sup>、肝窦毛细血管化<sup>[48,49]</sup>、肝实质细胞的缺血缺氧<sup>[43,44]</sup>、肝细胞的再生<sup>[30,50]</sup>等, 目前已证实的与肝纤维化病理过程相关的基因有数十种之多, NDRG2是其中的一种<sup>[30]</sup>, 其与肝纤维化的多个病理过程相关. 目前研究发现, NDRG2基因通过阻断TGF- $\beta$ 1/Smad信号通路, 抑制肝星形细胞的活化和促进肝细胞外基质的降解; 通过诱导p53和p21调节Bax/Bcl-2升高, 同时抑制cyclin E-Cdk2表达, 促进肝细胞生长; 作为HIF-1的下游基因, 减轻肝细胞缺氧应激损伤等途径抑制肝纤维化. NDRG2在正常组织、良性肿瘤、恶性肿瘤中的表达水平逐渐降低<sup>[30,31,33]</sup>, 其与组织缺氧程度呈负相关<sup>[47]</sup>, 并且在肝脏再生过程中呈动态变化<sup>[33,34]</sup>. NDRG2通过阻断ERK1/2信号通路, 抑制MMP2、MMP9表达, 减少对癌细胞细胞外基质的降解, 降低肝细胞癌的侵蚀转移能力<sup>[31,51,52]</sup>, 而在肝纤维化病理过程中, NDRG2能够促进MMP表达、同时抑制TIMP表达, 改变MMP/TIMP比例, 促进肝细胞外

基质的降解, 抑制肝纤维化的进展<sup>[11,30]</sup>. NDRG2对MMP的调节作用, 在不同病理过程中截然相反, 可能与疾病本身的病理特点及通过影响不同的信号通路有关, 目前缺乏针对此现象的研究报道. 肝损伤过程中是否存在NDRG2表达水平的动态演变, 其变化对早期判断疾病预后是否具有指导性, 仍值得进一步探讨. HSC的激活抑制NDRG2基因的表达, 慢性肝损伤激活HSC致肝纤维化逐渐加重的过程中, 是否同时存在NDRG2的动态演变有待进一步研究.

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## ■ 相关报道

长期以来NDRG2基因被认为是一种抑癌基因, 近年发现该基因广泛参与肝纤维的病理过程. NDRG2基因通过影响肝星形细胞(hepatic stellate cell)激活、调节MMP/TIMP、调节肝细胞生长等, 影响肝纤维化, 并且随着纤维化的进展, 肝细胞NDRG2基因表达下调.



## ■应用要点

- NDRG2基因与肝纤维化的多个病理环节密切相关, 并与肝纤维化的进展程度存在关联性, 为该病的诊断和治疗提供新的视角。
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## ■同行评价

NDRG2基因与肝纤维化发生相关性研究报道较少, 选题有新颖性。

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