世界华人消化杂志 2013年8月8日; 21(22): 2158-2163
ISSN 1009-3079 (print) ISSN 2219-2859 (online)

文献综述 REVIEW

细胞周期素依赖性激酶、细胞周期调控与肝纤维化

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■背景资料
目前认为肝纤维化发生的最终共同途径均是肝星状细胞(hepatic stellate cells, HSCs)活化. HSCs活化和增殖是肝纤维化的细胞学基础. 细胞周期的调控异常与HSCs过度增殖密切相关; 而细胞周期进程的实现依赖于细胞周期的内源性调控, 主要是通过磷酸化和去磷酸化为基础的周期素-周期素依赖性激酶(cyclin dependent kinase, CDK)抑制途径实现的.

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收稿日期: 2013-03-15 修回日期: 2013-06-03
接受日期: 2013-07-03 在线出版日期: 2013-08-08

Cyclin-dependent kinases, control of cell cycle and hepatic fibrosis

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Received: 2013-03-15 Revised: 2013-06-03
Accepted: 2013-07-03 Published online: 2013-08-08

Abstract
Multiple etiologies of liver disease lead to liver fibrosis by driving the activation of hepatic stellate cells (HSCs) into a myofibroblast-like phenotype that is contractile, proliferative and fibrogenic. Liver fibrosis is associated with the proliferation of HSCs, and the cell cycle of activated HSCs is abnormal. Cyclin-dependent kinases (CDKs) play essential roles in cell proliferation. However, the molecular mechanisms responsible for the abnormal proliferation of activated HSCs during hepatic fibrogenesis remain to be defined. Here we will review recent progress in understanding the associations among CDKs, the control of cell cycle and hepatic fibrosis, with an aim to reveal the potential mechanisms of hepatic fibrosis.

Key Words: Cyclin-dependent kinases; Control of cell cycle; Hepatic fibrosis

Wu D, Gu QH, Li ZW. Cyclin-dependent kinases, control of cell cycle and hepatic fibrosis. Shijie Huaren Xiaohua Zazhi 2013; 21(22): 2158-2163 URL: http://www.wjgnet.com/1009-3079/21/2158.asp DOI: http://dx.doi.org/10.11569/wcjd.v21.i22.2158

摘要
肝纤维化是多种肝脏疾病的共同病理学结局. 在肝纤维化过程中, 肝星状细胞(hepatic stellate cells, HSCs)发生活化, 表型发生改变, 使其具有收缩性、再生性, 并能生成胶原成分. 肝纤维化的发生发展与活化的HSCs的增殖情况有关; 而细胞增殖情况则与细胞周期素依赖性激酶、细胞周期调控密切相关. 但是, 目前对与此相关的分子机制尚未明确. 此综述就近年来与肝纤维化过程中细胞周期素依赖性激酶及细胞周期调控方面的研究加以总结, 以揭示可能存在的引起肝纤维化的部分机制.

关键词: 细胞周期素依赖性激酶; 细胞周期调控; 肝纤维化

核心提示: 通过对周期素依赖性激酶(cyclin dependent kinase, CDK)的结构、生物学功能、CDK与细胞周期调控, 以及CDK与肝纤维化发生、发展的关系进行总结, 阐明细胞周期调控及与之相关的信号转导途径对肝星状细胞激活、增殖、转化、凋亡的复制调控途径以及潜在的生物学功能, 进一步了解与肝纤维化有关的分子学机制, 助于寻找抗纤维化治疗的新途径.

吴丹, 谷秋红, 李智伟. 细胞周期素依赖性激酶、细胞周期调控与肝纤维化. 世界华人消化杂志 2013; 21(22): 2158-2163 URL: http://www.wjgnet.com/1009-3079/21/2158.asp DOI: http://dx.doi.org/10.11569/wcjd.v21.i22.2158

0 引言
肝纤维化的发生是各种原因导致的肝细胞损伤后肝脏内胶原活动性沉积的结果. 近年来的研究表明, 尽管不同病因致肝病的发病机制不同, 但肝纤维化发生的最终共同途径均是肝星状细

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胞(hepatic stellate cells, HSCs)活化. HSCs活化和增殖是肝纤维化的细胞学基础, 是各种病因肝纤维化发生的中心环节. 而细胞周期的调控异常与HSCs过度增殖密切相关. 细胞周期进程的实现依赖于细胞周期的内源性调控, 主要是通过磷酸化和去磷酸化为基础的周期素-周期素依赖性激酶(cyclin dependent kinase, CDK)抑制途径实现的. 现将CDK的结构、生物学功能及其与细胞周期调控及肝纤维化发生、发展的关系进行总结, 以助于进一步了解与肝纤维化有关的分子学机制.

1 细胞周期素依赖性激酶

真核细胞的细胞(体细胞)分裂周期(cell division cycle, CDC)是由S期(DNA合成期)、M期(有丝分裂期)以及两个间期-G_1期(DNA合成前期)和G_2期(DNA合成后期)这4个阶段组成. 细胞周期的循环运转是受一系列磷酸化/去磷酸化事件调控, 参与调控的分子成员由一组丝氨酸/苏氨酸蛋白激酶组成催化亚单位和属于细胞周期素家族成员的调节亚单位细胞周期素组成. 由于这些激酶需要与细胞周期素结合才具有激酶活性, 因此被称为CDK[1,2].

目前已发现在单核真核细胞生物中, 负责细胞内蛋白质磷酸化的CDK通常只有一种, 在芽殖酵母中是CDC28, 在裂殖酵母中是CDC2[2-4]. 在多细胞真核生物中参与细胞周期的CDK有7个成员, 即CDK1-7, 他们分别调控着细胞周期中不同阶段及细胞周期的进程[1,2,5-8]. 目前研究已证实, 7种CDK分子彼此在DNA序列上的同源性超过40%, 其蛋白产物相对分子量为30×10^3-40×10^3, 有一个催化核心, 均属丝氨酸和苏氨酸激酶[9]. 其中: (1)CDK1是CDC基因(CDC2)编码的蛋白, 相对分子量为34×10^3, 是一种丝氨酸蛋白激酶, 主要与cyclinA和B结合构成细胞M期促进因子, 推动细胞进入M期; (2)CDK2的DNA全长879个碱基, 编码298个氨基酸的蛋白质, 可分别与周期素E、周期素A和周期素D结合, 分别在G_1/S期、S期和G_2期发挥作用; (3)CDK4基因位于12q13-14, 编码分子量为33×10^3 kDa的蛋白质, *CDK6*基因定位于7q21-22, 编码分子量为38×10^3 kDa的蛋白质, 二者结构及功能相似, 是G_1期运行的重要分子, 可与周期素D结合, 通过周期素D-CDK4/CDK6通路调控细胞越过G_1期限制点; (4)CDK5主要存在于脑内. CDK5蛋白由292个氨基酸组成, 相对分子量为分子量为33×10^3, 与人CDC2和CDK2的同源性分别为58%和62%; (5)CDK7能与周期素H相互作用, 结合形成活性复合物, 也被称为CDK活化激酶, 他能够使细胞周期调控中的所有主要的CDK磷酸化.

2 CDK与细胞周期调控

目前认为, CDK在细胞周期调控网络中处于中心地位, 主要生物学作用是调控细胞周期的不同时相, 从G_1、S、G_2到M期, 完成循环[10-12]. CDK激活有赖于与cyclin的结合和其分子中某些氨基酸残基的磷酸化状态. 含催化亚基的CDK需要cyclin提供调节亚基才能显示活性, 只有cyclin浓度升高达到阈值时, 才能与相应的CDK结合形成cyclin-CDK复合体, 这时CDK才能被激活; CDK分子中含有活化部位和抑制部位, 只有前者处于磷酸化而后者处于去磷酸化状态, CDK才显活性[13]. CDK的活性还受其上游的CDK活化激酶(CDK-activating kinase, CAK)的影响. CAK正是通过使CDK分子中的活化部位的氨基酸残基磷酸化来参与调控CDK的活性的[14].

细胞周期的不同时相, 会有不同CDK发生活化, 来调控细胞周期的运行. 活化的CDK呈现出蛋白激酶的活性, 使不同的底物蛋白磷酸化, 从而启动或调控细胞周期的主要事件. CDK激活的底物主要有视网膜神经胶质瘤蛋白、抑癌基因*p107*、*p103*等, 具有促进细胞周期时相转变、启动DNA合成、运行细胞分裂、推进细胞周期运行的重要功能[9,11,12].

研究发现, CDK1是及其调节亚基-周期素构成的细胞M期促进因子, 推动细胞进入M期, 在细胞周期的调控中其决定性作用. CDC2是细胞中唯一能够在细胞周期由G_1期→S期和由G_2期→M期转变中的两个调控点均起作用的基因. CDK1激酶的激活是细胞分裂、增殖的信号, 有启动DNA复制和诱导细胞有丝分裂的双重作用. 有研究发现, 对于某些物种, CDK1是其生存所必需的CDK分子[15-18].

CDK2可分别与周期素E、周期素A和周期素D结合, 分别在G_1/S期、S期和G_2期发挥作用. CDK2是启动DNA复制的关键激酶, 也是G_2期运行的必要条件[16,19-23]. CDK4和CDK6是G_1期运行的重要分子, 可与周期素D结合, 通过周期素D-CDK4/CDK6通路调控细胞越过G_1期限制点[24-27]. 既往研究已证实, 尽管CDK2/CDK4与CDK6不是小鼠细胞所必需的, 但他们对于某些

■研发前沿

现在已发现很多肿瘤都存在CDK表达异常, 在肿瘤中往往存在一种或多种CDK的扩增和过表达现象. 相对而言, 我们对肝纤维化过程中CDK的基因及其表达产物生物学作用的了解还比较少, 对于与HSCs增殖相关的准确机制目前还不十分明确.

■相关报道
目前CDK及细胞周期调控方面的研究大多针对于肿瘤的发生机制及治疗, 肝纤维化的研究涉及到CDK及细胞调控方面的还比较少, 希望本篇综述能在肝纤维化机制及治疗方面带给我们更多提示.

特殊类型的细胞还是非常重要的. 例如, CDK2参与调控生殖细胞的增殖、CDK4参与调控胰岛β细胞和脑垂体泌乳细胞的增殖; 而CDK6则与血液细胞的增殖密切相关[26-31].

CDK5主要存在于脑内, 可与Cdc激酶有高度同源性, 也可以与周期素D1、D2结合, 但结合后没有激酶活性, 与Cdc也没有关系, 但参与神经系统发育[32].

CDK7与周期素H相互作用结合所形成的CDK活化激酶, 能够使细胞周期调控中的所有主要的CDK-周期素底物磷酸化而被激活, 能引起的某一种CDK周期底物的磷酸化, 与周期素的时相起伏相平行. 已有实验结果证实, 细胞周期阻滞以及凋亡程度与CDK7的蛋白表达水平有一定的关系[33,34].

CDK的灭活, 除了泛素介导的蛋白水解体系外, CDI即CDK抑制物(CDK inhibitor, CDI)也可特异性抑制CDK的活性. 哺乳类动物的CDI主要包括Ink4和Kip或称Cip或Waf1. 前者是一组CDK4的抑制蛋白, 其成员包括P16Ink4a、P15Ink4b、P18Ink4c、P19Ink4d, 可特异性地与CDK4/6结合, 阻止其与cyclin再结合, 抑制其激酶活性, 在S期达高峰, 是G_1/S限制点负调控机制的重要组成部分. 后者成员包括P21Kip1、P27Kip1、P57Kip2, 他们可特异性抑制几种cyclinD/CDK的蛋白激酶活性, 主要调控细胞周期确保遗传物质精确地传递给下一代[33,35,36].

细胞要想在细胞周期过程中通过G_1/S检查点, CDK2、CDK4和CDK6必须发生活化. CDK4和CDK6与细胞周期素D结合后可以被活化, 而CDK2则需要与细胞周期素E结合才能被活化. CDK4、CDK6和细胞周期素D的表达在G_1期早期就开始增加, 并对G_1期晚期CDK2和周期素E的合成进行调控. Rb蛋白在G_1期可被活化的CDK持续磷酸化, 并释放核转录因子E2F, 这就使细胞对DNA合成的抑制作用消失, DNA合成启动, 促进细胞由G_1期向S期转化[2,11,14,18,22].

3 肝纤维化过程中的HSCs细胞周期调控

肝纤维化是多种肝脏疾病的共同病理学结局[37]. 目前认为, 肝纤维化发生的中心事件是: 由损伤引起的HSCs激活并转化为肌成纤维样细胞, 通过旁分泌与自分泌作用, 使HSCs增殖, 合成大量的细胞外基质. 细胞外基质的分泌增加, 降解减少, 以致其在肝脏内大量沉积, 最终导致肝纤维化. Yuan等[38]将这一过程归纳为4个连续又部分重叠的阶段: (1)炎症反应的发生和HSCs激活启动; (2)局部ECM的改变; (3)损伤部位肌成纤维细胞的迁移、聚集和增殖, 随后出现血管的生成和上皮增殖; (4)损伤愈合后瘢痕的收缩.

在肝纤维化发生、发展的过程中, 活化的HSCs发生了角色转换, 这也是肝纤维化得以不断进展的关键步骤. 活化的HSCs不再是正常肝脏中的贮脂细胞, 而成为了肝脏中细胞外基质成分的主要细胞来源[39-45]. 除了在功能上的改变, 在肝纤维化过程中, HSCs还出现大量增殖的情况, 以致其细胞数量明显增加, 这意味着其细胞周期的调控出现了异常; 也可以说, 在HSCs活化后, 调节其细胞周期运行的相关的cyclin、CDK及CDI可能在表达及功能等方面出现了异常[42,44-46].

目前认为, 活化的HSCs出现了不同于正常生理状态下的增殖异常活跃的状态. 有研究表明, 受到乙醛刺激的HSCs增殖活跃, 其细胞周期素D1与CDK4的mRNA的表达都有所增加, 而有丝分裂原信号调节激酶-1的特异性抑制物能够明显抑制HSCs内这两种mRNA的表达, 同时HSCs的增殖被明显抑制了, 说明cyclinD1与CDK4参与了HSCs的增殖, 而ERK通路可能参与了对cyclinD1与CDK4 mRNA表达的调节[47,48]. 而在对小鼠肝纤维化的研究中发现, cyclinE参与调控小鼠HSCs的增殖, 对小鼠肝纤维化的形成非常重要[49].

而在对某些具有转录因子抑制作用的药物的研究中(如curcumin)发现, 这类药物可以抑制HSCs表达cyclinD1, 而HSCs的增殖也被抑制, 并发生凋亡[50-52]; 还有一些药物, 如川芎嗪可以通过对体外HSCs内ERK/P53信号转导的调节来阻止G_0/G_1期细胞进入细胞周期的下一时相, 并能诱导HSCs的凋亡[53]. 而某些CDK的抑制物则与人非肿大性肝炎或肝硬化向肝细胞癌转化有关[54]. 此外还有研究发现, 多种肽类及信号转导分子, 诸如核因子-κB、转化生长因子-β、肿瘤坏死因子-α等都参与了对HSCs增殖的调控[55-57].

4 结论

我们已经知道, 细胞周期的调控主要是通过CDK的一系列磷酸化和去磷酸化反应来完成的. 细胞周期素能使CDK发生磷酸化, 在这一过程起到正调节作用, 而CKI则使CDK去磷酸化, 抑制CDK的活性. 因此, 可以说细胞周期的内源

性调控的核心机制是CDK活性的表达与调控. *CDK*基因及其表达产物的异常改变可使细胞出现增殖过度. 而目前对于因*CDK*基因及其表达产物异常的研究多数都致力于肿瘤发生、发展等研究领域, 现已发现很多肿瘤都存在CDK表达异常, 在肿瘤中往往存在一种或多种CDK的扩增和过表达现象. 相对而言, 我们对肝纤维化过程中*CDK*基因及其表达产物生物学作用的了解还比较少, 对于与HSCs增殖相关的准确机制目前还不十分明确, 相关的研究也比较少, 而HSCs活化、增殖或凋亡是肝纤维化发生、发展或恢复的决定因素, 进一步阐明细胞周期调控及与之相关的信号转导途径对HSCs激活、增殖、转化、凋亡的调控以及潜在的生物学功能将有助于寻找抗纤维化治疗的新途径.

■**创新盘点**

CDK及其抑制剂的作用与肿瘤细胞增殖有密切关系, 但他与肝纤维化关系的研究较少.

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■同行评价
CDK及其抑制剂的作用与肿瘤细胞增殖有密切关系, CDK抑制剂是近年研究热点, 但他与肝纤维化的研究较少, 本文对此进行探讨有一定的创新性和研究价值.

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编辑 田滢 电编 闫晋利

ISSN 1009-3079 (print) ISSN 2219-2859 (online) DOI: 10.11569

• 消息 •

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