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文献综述 REVIEW

非酒精性脂肪性肝病与肝细胞凋亡调控机制的研究进展

陈少东, 胡义扬

陈少东, 胡义扬, 上海中医药大学附属曙光医院 上海中医药大学肝病研究所 上海市 201203
陈少东, 厦门大学医学院 福建省厦门市 361005
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作者贡献分布: 陈少东与胡义扬对此文所作贡献均等.
通讯作者: 胡义扬, 201203, 上海市浦东新区张衡路528号, 上海中医药大学附属曙光医院; 上海中医药大学肝病研究所. yyhu@citiz.net
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Advances in regulation mechanism of hepatocyte apoptosis in nonalcoholic fatty liver disease

Shao-Dong Chen, Yi-Yang Hu

Chen Shao-Dong, Hu Yi-Yang, Shuguang Hospital Affiliated to Shanghai University of Traditional Chinese Medicine; Institute of Liver Disease, Shanghai University of Traditional Chinese Medicine, Shanghai 201203, China
Supported by: National Natural Science Foundation of China, No. 30672635, and the Shanghai Leading Academic Discipline Project, No. Y0302
Correspondence to: Yi-Yang Hu, Shuguang Hospital Affiliated to Shanghai University of Traditional Chinese Medicine; Institute of Liver Disease, Shanghai University of Traditional Chinese Medicine, 528 Zhangheng Road, Pudongxin District, Shanghai 201203, China. yyhu@citiz.net
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Abstract

The pathogenic mechanism of nonalcoholic fatty liver disease (NAFLD) still remains unclear. In recent years, many studies indicate that abnormal hepatocyte apoptosis exists in NAFLD, confirming the close relationship between NAFLD and hepatocyte apoptosis. The regulation of cell apoptosis includes two: positive or negative. In this paper, we review the research advances in the regulation of hepatocyte apoptosis during the pathogenesis of NAFLD.

Key Words: Nonalcoholic fatty liver disease; Cell apoptosis; Liver cell

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摘要

非酒精性脂肪性肝病的发病机制至今尚不十分清楚. 近年来众多研究表明, 本病存在肝细胞凋亡的异常, 说明肝细胞凋亡与本病的发生密切相关. 调控细胞凋亡的机制可分正向/负向两个方面的调控因素. 本文就近几年在非酒精性脂肪性肝病肝细胞凋亡调控机制方面的研究进展作一综述.

关键词: 非酒精性脂肪性肝病; 细胞凋亡; 肝细胞

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0 引言

目前在非酒精性脂肪肝病(nonalcoholic fatty liver disease, NAFLD)的发病机制中, Day *et al*提出的二次打击学说得到公认. 然而随着对凋亡的研究, 不断有证据表明在NAFLD中, 凋亡起着重要的作用[1-2]. 如范建高 *et al*在肥胖高脂血症性脂肪性肝炎细胞凋亡的动物实验研究中, 发现非酒精性脂肪性肝炎(nonalcohlic steatohepatitis, NASH)在肝细胞坏死增加的同时, 也存在肝细胞凋亡显著增加的现象[3]. 而Nitchell *et al*也发现在酒精性肝炎和非酒精性肝病以及相关的肝纤维化中, 均有明显的肝细胞凋亡现象发生[4-5]. 那么肝细胞凋亡在NAFLD中受到哪些相关因素的调控, 而这些因素又是如何具体调控肝细胞凋亡呢? 具体来说, 肝细胞凋亡受到正向/负向两个方面的调控因素的作用, 具体可以分为以下两类: (1)正向调控肝细胞凋亡的因素, 包括野生型p53、Bax、TNF-α、Fas等; (2)负向调控肝细胞凋亡的因素, 如Bcl-2、NF-κB等. 我们这里对近几年在NAFLD发病过程中参与调控肝细胞凋亡的有关因素及其作用机制作一综述.

1 正向调控肝细胞凋亡的相关因素

1.1 Fas Fas属于肿瘤坏死因子(tumor necrosis factor, TNF)受体家族成员, Fas基因编码一种相对分子质量为48 kDa的跨膜蛋白. Fas在各种

■背景资料
目前在非酒精性脂肪肝病(NAFLD)的发病机制中, Day *et al*提出的二次打击学说得到公认. 然而随着对凋亡的研究, 不断有证据表明在NAFLD中, 凋亡起着重要的作用. 肝细胞凋亡是一个多基因调控的复杂过程, 各基因在调节细胞凋亡的过程中, 不是孤立的, 而是通过某些环节相互影响, 共同调节凋亡的实施.

■同行评议者
李军祥, 教授, 北京中医药大学附属东方医院消化内科

■研发前沿
非酒精性脂肪性肝病存在肝细胞凋亡的异常, 说明肝细胞凋亡与本病的发生密切相关, 但具体机制至今尚不清楚.

组织中均可表达, 尤其在肝脏、胸腺、心脏、肾脏中表达的量很大. Fas配体(FasL)主要表达于活化的T细胞, NK细胞. 表达Fas抗原的细胞与Fas配体结合可活化天冬半胱酶(caspase)从而引起细胞凋亡. 研究表明病毒性肝炎和人类其他一些肝病可由Fas受体诱导引起肝细胞凋亡[6-7]. 而Riberio *et al*发现在NASH以及酒精性脂肪性肝炎(alcoholic steatohepatitis, ASH)中, 可见Fas受体介导的肝细胞凋亡[8]. 同时研究证实Fas在NASH患者肝脏内表达增加, 他不仅可以传导凋亡信号, 还通过caspase-8裂解Bid损伤线粒体[9]. Jaeschke *et al*[10]发现Fas介导细胞凋亡的机制在于Fas受体在胞质中的尾部含有一个“死亡域”序列, 可以与Fas相关死亡域蛋白(fas-associated death domain protein, FADD)结合, 结合之后吸引caspase-8前体形成死亡激发信号复合体(death inducing signaling complex, DISC). 一旦DISC形成, caspase-8前体自身催化成有活性的caspase-8并释放. caspase-8是上游的一个活化caspases, 他能对下游的一些效应caspases如caspase-3进行加工, 最终导致细胞凋亡[11-12]. 正如史洪涛 *et al*在NAFLD大鼠实验中, 发现随着肝细胞凋亡的升高, caspase-3的量也相应的增加, 说明caspase-3介导的肝细胞凋亡可能是脂肪肝发病过程中肝细胞损伤的重要机制[1,13]. 而相反, NAFLD大鼠在罗格列酮与二甲双胍的治疗下, 其Fas mRNA表达水平却显著下降[14].

1.2 野生型*P53*(*WTP53*) *WTP53*基因是典型的抑癌基因, 位于17号染色体, 11个外显子和10个内含子, 编码一个由393个氨基酸组成的相对分子质量为53 kDa的核内磷酸蛋白, 故称为p53. p53蛋白具有蛋白-DNA和蛋白质-蛋白质结合的特性, 其功能形式为四联体[15]. *P53*基因分为野生型*P53*和突变型*P53*, 研究表明*WTp53*具有明显的促肝细胞凋亡的作用, 而且主要通过转录、激活及抑制特定的蛋白和抗凋亡基因来实现[16]. *P53*基因在调控肝细胞凋亡的过程中, 主要是在细胞分裂的G_1/S期调控点起作用, 以决定细胞是否启动DNA合成还是进入凋亡[17-18]. 当DNA受损后, *P53*基因表达增强, p53蛋白积累在细胞中, 使肝细胞停滞于G_1期, 使之在复制前修复损伤的DNA, 修复后细胞进入S期; 一旦损伤严重, 则p53蛋白持续增高, 诱发细胞凋亡以防受损的DNA复制. p53在调控肝细胞凋亡的过程中, 与p21蛋白协同作用, p21蛋白是一个通用的细胞周期依赖激酶的抑制因子, 在细胞分裂G_1期, p53就激活p21蛋白与之共同调控肝细胞是复制还是凋亡. 如Ikeda *et al*发现p53在脂肪肝发病中起重要作用, 并且与p21共同起协调作用[18-19].

1.3 *Bax* *Bax*是第一个确定为*Bcl-2*的同源基因, 他和Bcl-2基因具有40%的同源性, 编码相对分子质量为21 kDa的Bax蛋白, 其蛋白包括家族特征的BH1、BH2、BH3结构域, 此外还有c末端的跨膜结构域. 如Mengshol *et al*发现在丙型肝炎并发脂肪肝患者中, 出现Bax升高现象, 提示出现肝细胞凋亡[20-22]. Bax发挥促进凋亡的机制有三, 其一, 是Bax蛋白本身可形成同二聚体, 促进细胞凋亡[23-24]. 其二, 如Malhi发现在游离脂肪酸诱导下的NAFLD细胞模型中, Bax作为线粒体功能失调的调解者, 其活化可介导c-Jun氨基末端激酶(JNK)依赖的脂质凋亡, 当JNK活化仅带有BH3结构域蛋白的Bim, 可观察到Bax活化并发生脂质凋亡, 相反运用RNA干扰技术可使仅带有BH3结构域蛋白的Bim表达降低, 同时也会抑制Bax的活化并减少脂质凋亡[25-26]. 第三, Kaus-Michacl还提出Bax从胞质中移位到线粒体外膜上, 并在此形成微孔结构的低聚物, 从而促进细胞色素C的释放. 细胞色素C与凋亡蛋白活化因子-1(Apaf-1)、dATP及caspase-9前体结合形成凋亡小体而发生凋亡[27-29].

1.4 TNF-α Sato *et al*发现脂肪肝中TNF-α的上调可引起线粒体膜通透性改变并引起凋亡发生[30-31], 其机制在于TNF受体有TNFR1和TNFR2两种. TNF-α与TNFR1结合, TNFR1形成三聚体后与TNF受体偶连的死亡域(TNFR-associated death domain, TRADD)通过死亡结构蛋白的相互作用, 再与FADD结合从而激活caspase-8, 再激活caspase-3引起细胞凋亡[32-34], 或者通过TRADD结合后TRAIDD(RIP-associated Ich/CED-3 homologous with a death domain)通过死亡域与RIP连接, 并使caspase-2聚集与RIP进一步引起细胞凋亡[35-37].

2 负向调控肝细胞凋亡的相关因素

2.1 *Bcl-2* *Bcl-2*基因是从滤泡性B淋巴细胞中分离出来的一种癌基因, 正常位于18号染色体上, 但在淋巴瘤中却异位转移到14号染色体上[38]. *Bcl-2*基因编码一个相对分子质量为25-26 kDa的蛋白, 其C末端的21个疏水氨基酸组成一个延伸的键状结构, 这个键状结构可插入细胞的膜结构中[39]. 研究发现, *Bcl-2*在肝细胞凋亡的基因调控中起重要作用, 通过抑制细胞凋亡来延长

细胞存活的时间, 因此又称为“生存基因”[40]. 但是在NAFLD的发病中, *Bcl-2*的表达均显著下降[41], 如在丙型肝炎并发脂肪肝患者中, Bcl-2 mRNA水平显著下降, 说明*Bcl-2*抑制肝细胞凋亡的作用不明显[42].

2.2 NF-κB NF-κB是细胞凋亡负向调控家族中的一名重要成员, 他最早是在1986年被定义为与免疫球蛋白轻链基因增强子κB序列(GGGACTTTCC), 几乎存在于所有类型的细胞中, 但却是与其抑制物IkBs结合, 以不活化形式存在于胞质中[43]. NF-κB是Rel蛋白成员, 已发现哺乳动物有5种NF-κB/Rel蛋白, 分别是NF-κB1(p50)、NF-κB2(p52)、C-Rel、Re1A(p65)、RelB, 他们之间可以形成多种形式同源或异源二聚体[44]. Antwerp发现NF-κB能够抑制TNF-α诱导的细胞凋亡[45]. 之后又陆续发现活化的NF-κB能阻碍多种类型细胞的凋亡[46], 这种作用Wang认为是通过一系列与凋亡蛋白酶相作用的抗凋亡蛋白(TRAF1、TRAF2)及凋亡抑制蛋白(C-IAP1、C-IAP2)来实现的[47]. NF-κB诱导他们的表达从而抑制caspase-8的活化, 而caspase-8是介导死亡受体相关信号必须的凋亡蛋白酶, 也就是说NF-κB活化发挥抗凋亡机制是在激发阶段而不是执行阶段来阻断死亡信号[48-49]. 另外NF-κB还可以通过诱导抗凋亡基因的表达来发展抗凋亡作用. 有文献报道, *Bcl-2*基因的bfl-1启动子含有一个NF-κB的结合位点, *Bcl-2*基因的表达依赖于NF-κB的活性[50]. Wang *et al*证实活化的NF-κB可通过激活Bcl-2家族成员A1/bfl-1表达而阻断caspase-3激活, 并抑制线粒体释放细胞色素C[51]. 在NASH中, 增多的ROS可通过磷酸化泛素化作用和蛋白酶体介导使IκB降解, 激活NF-κB开始转录, 产生抗凋亡效应[52]. Riberioo *et al*发现在NASH以及ASH中, 可见凋亡与NF-κB活化表达有关[53]. 当使用NF-κB抑制剂后, 会明显抑制NF-κB以及其靶基因*Bcl-xL*的活性, 从而提高由TNF-α诱导的细胞凋亡[54-55].

3 正负调控相关因素的相互作用

肝细胞凋亡是一个多基因调控的复杂过程, 各基因在调节细胞凋亡的过程中, 不是孤立的, 而是通过某些环节相互影响, 共同调节凋亡的实施. 如Bax与Bcl-2在调控肝细胞凋亡的过程中相互作用, 共同参与调节肝细胞凋亡[56]. Bcl-2与Bax可形成同二聚体或异二聚体来改变线粒体的通透性, 从而决定细胞的生存与死亡. 当Bcl-2相对量高于Bax时, 则Bcl-2同二聚体增多, 并促进形成Bcl-2-Bax异二聚体, 而Bcl-2同二聚体和Bcl-2-Bax异二聚体都可抑制细胞凋亡; 相反当Bax的量相对高于Bcl-2时, 则Bax同二聚体增多, 从而促进细胞凋亡[40]. 因而Bcl-2/Bax两蛋白之间的比例是决定细胞凋亡或存活的关键因素[57-58]. 除此以外Bcl-2还可以通过直接或间接的影响细胞信号传递蛋白, 如抑制*WTp53*介导的细胞凋亡[59-60]; *WTp53*在诱导细胞凋亡的过程中, 能降低细胞内源性Bcl-2蛋白的表达并抑制其功能, 提高细胞内Bax蛋白的表达, 使Bax/Bcl-2的比例失调而促进细胞凋亡[59-62]; 再者Fas mRNA的表达也与caspases的活性密切相关[63-65].

肝细胞凋亡参与NAFLD的发病机制已经得到肯定[66], 但是由于肝细胞凋亡是一柄双刃剑, 有必要对具体的调控环节, 特别是各种调控因素之间的关系进行深层次的研究, 以期对其发病机制有新的认识, 以寻求新的治疗方案.

■**相关报道**
范建高 *et al*在肥胖高脂血症性脂肪性肝炎细胞凋亡的动物实验研究中, 发现非酒精性脂肪性肝炎(NASH)在肝细胞坏死增加的同时, 也存在肝细胞凋亡显著增加的现象.

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■应用要点
本文对肝细胞凋亡参考NAFLD的具体调控环节, 特别是各种调控因素之间的关系进行深层次的研究, 以期对其发病机制有新的认识, 以寻求新的治疗方案.

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■同行评价
本文内容全面, 论述条理, 语言流畅, 总体写的很好, 具有一定的参考价值.

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