

细胞凋亡在非酒精性脂肪性肝病中的作用

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Role of hepatocyte apoptosis in non-alcoholic fatty liver disease

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Abstract

Non-alcoholic fatty liver disease (NAFLD) represents a clinicopathologic syndrome, characterized mainly by macrovesicular hepatic steatosis in the absence of significant alcohol ingestion and excluding other liver diseases. With the improvement of lifestyle, living habit and dietary choices, obesity and diabetes are becoming epidemic, subsequently increasing the risk for developing NAFLD. But the pathogenesis of NAFLD remains poorly understood yet. Recent research indicate that hepatocyte apoptosis and related factor such as Fas/FasL system, tumor necrosis factor (TNF) family, Bcl-2 family, Caspases, nuclear factor- κ B (NF- κ B), cytochrome C, and cathepsin B are abnormally over-expressed in NAFLD. Apoptosis is one of the most important mechanisms leading to hepatocyte elimination, liver injury, inflammation and fibrosis in NAFLD. In this article, we reviewed the progress in the role of hepatocyte apoptosis in NAFLD.

Key Words: Non-alcoholic fatty liver; Non-alcoholic

steatohepatitis; Apoptosis

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摘要

非酒精性脂肪性肝病(non-alcoholic fatty liver disease, NAFLD)是指除外酒精和其他明确的损肝因素所致的,以弥漫性肝细胞大泡性脂肪变为主要特征的临床病理综合征。随着生活水平的提高、生活习惯、饮食结构的改变,肥胖和糖尿病的发病率增加,NAFLD的发病率呈上升趋势,严重危害人民健康。而非酒精性脂肪性肝病的发病机制仍不十分清楚,最近研究表明细胞凋亡及其相关因素Fas系统、TNF家族、Bcl-2蛋白家族、Caspases蛋白酶家族、NF- κ B、细胞色素C及组织蛋白酶B等在NAFLD中表达异常增多,说明肝细胞凋亡在NAFLD的发生进展中扮演了至关重要角色。本文就这方面的研究进展作一综述。

关键词: 非酒精性脂肪性肝病; 非酒精性脂肪性肝炎; 细胞凋亡

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0 引言

非酒精性脂肪性肝病(non-alcoholic fatty liver disease, NAFLD)是指除外酒精和其他明确的损肝因素所致的,以弥漫性肝细胞大泡性脂肪变为主要特征的临床病理综合征^[1-2]。NAFLD包括单纯性脂肪肝及由其演变的非酒精性脂肪性肝炎(non-alcoholic steatohepatitis, NASH)和NASH相关性肝纤维化、肝硬化,是一类与遗传-环境-代谢应激相关的肝脏疾病谱^[3-4]。NAFLD的发病机制至今仍未完全阐明,近年来关于肝细胞凋亡在其发生发展中的作用取得较大进展,揭示了肝细胞凋亡在NAFLD向NASH,及肝纤维化乃至肝硬化、肝癌进展中扮演的至关重要角色^[5-7]。

■背景资料

随着生活水平的提高、饮食结构的改变,非酒精性脂肪性肝病(NAFLD)的发病率呈逐年上升趋势,严重危害人民健康。NAFLD与肝功能衰竭、肝硬化、肝癌密切相关,且NAFLD患者罹患糖尿病、高血压、心脑血管事件的概率比普通人群高。因而其诊断和治疗成为肝病研究的热点,近年来研究表明肝细胞凋亡直接或间接促进了肝脏炎症与纤维化,与NAFLD的发生进展密切相关。

■同行评议者

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■ 研发前沿

肝细胞凋亡及相关调节因素在NAFLD的发病及其进展机制中的作用是目前NAFLD研究的热点之一,临床中对NAFLD患者无创及特异的诊断指标及抗凋亡治疗NAFLD的疗效和安全性的评价也成为临床研究NAFLD的热点与重点。

1 细胞凋亡

1.1 概述 细胞凋亡(apoptosis)是指为维持内环境稳定,由基因控制的机体正常细胞在受到生理和病理性刺激后出现的一种自发的死亡过程,是一个主动、高度有序、基因控制、信号依赖及一系列酶参与的过程。最早是1972年由Kerr根据形态学特征首先提出的^[8]。细胞凋亡的形态学特征表现为:(1)细胞表面的特化结构如微绒毛的消失,细胞膜仍保持完整性;(2)核染色质断裂为大小不等的片段,与某些细胞器如线粒体一起聚集,为反折的细胞膜所包围,形成单个的凋亡小体(apoptotic bodies),核DNA被核酸酶降解为规则的DNA片段,电泳呈特殊的梯状区带(ladder);(3)凋亡小体逐渐为邻近的吞噬细胞所吞噬消化^[9-10]。凋亡是一柄双刃剑,生理状况下的肝细胞凋亡参与调节正常肝细胞数量,维持肝脏正常体积,在肝脏发育和内稳态起重要作用,是肝细胞对抗感染、肿瘤及防止自身免疫反应的卫士;而病理条件下的肝细胞凋亡则是造成肝脏损伤和肝脏疾病最基本的中心环节,病毒性肝炎、酒精性肝病、NAFLD、自身免疫性肝炎、肝纤维化、移植排斥性肝炎等肝病的发病机制均与肝细胞凋亡有密切关系^[11-14]。

1.2 肝细胞凋亡途径和相关调控机制

1.2.1 死亡受体信号转导通路:在肝脏中明确表达的死亡受体包括Fas/FasL, TNF- α /肿瘤坏死因子受体-1(TNFR-1),肿瘤坏死因子相关的诱导凋亡配体受体(TRAIL-R1和TRAIL-R2)^[15-16]。Fas配体与Fas受体结合后聚成三聚体启动凋亡信号的转导, Fas受体在胞质中的尾部含有一个“死亡域(death domain)”序列,可与Fas相关死亡域蛋白(fas-associated death domain protein, FADD)结合使procaspase-8、细胞型Fas相关死亡域样白介素-1 β 转换酶抑制蛋白(cellular FADD-like interleukin-1 β converting enzyme inhibitory protein, c-FLIP)在细胞内受体区域募集,形成死亡诱导信号复合体(death-inducing signaling complex, DISC),激活procaspase-8,引起上游启动Caspase-8释放,导致下游效应Caspase-3、-6、-7等激活,触发Caspase级联反应,导致细胞凋亡^[17-18]。TRAIL-R1和TRAIL-R2诱导凋亡途径与此类似^[19]。TNF-R1与TNF- α 结合后,其死亡域募集TNF受体形成由肿瘤坏死因子受体1相关死亡结构域(TNFR1-associated death domain, TRADD),死亡域结合受体反应蛋白(receptor inducing protein, RIP)和TNF受体相关因子-2(TRAF-2)组

成的复合物I。复合物I与TNF-R1分离并在胞质溶胶中形成包含FADD, c-FLIP, 凋亡抑制蛋白1/2(c-IAP1/2)的DISC(复合物II)使Caspase-8活化触发Caspase级联反应。然而,在肝细胞中此Caspase-8复合物的活性相当微弱,需要经过线粒体途径使凋亡得以信号放大^[20-21]。细胞内没有形成足够量的DISC,激活的procaspase-8不足以引起蛋白水解酶的级联反应时, Caspase-8可以切割Bid(一种仅含BH3结构域的Bcl-2家族蛋白)形成活性片段tBid。tBid随后引起线粒体嵴重组,激活Bax及Bak相互作用引起线粒体通透性(mitochondrial permeability transition, MPT)的改变,使细胞色素C和第二个线粒体来源的胱氨酸酶激活剂/低等电点IAP直接结合蛋白(second mitochondrial-derived activator of caspase/direct IAP-binding protein with low pi, Smac/Diablo),凋亡诱导因子(apoptosis inducing factor, AIF)释放^[22]。因此,死亡受体能通过Caspase-8裂解Bid损伤线粒体,进入线粒体途径,使内外两条途径得以联合^[23]。

1.2.2 线粒体信号通路:线粒体跨膜电位消失使MPT开放释放细胞色素C和Smac/Diablo,细胞色素C在细胞质中dATP存在的条件下能与凋亡蛋白活性因子-1(Apaf-1)及procaspase-9结合成高分子量复合物,促使Caspase-9与其结合形成凋亡体(apoptosome),Caspase-9被激活再激活Caspase-3、-7级联反应^[24-25]。此外,释放出来的Smac/Diablo与X-连锁凋亡抑制蛋白(XIAP)结合,使其对Caspase-9和Caspase-3的抑制作用减弱,进而导致Caspase-9和Caspase-3的充分激活^[26]。至此,内外两条途径最终统一于线粒体的级联放大信号,从而降解细胞内成分^[27]。

1.2.3 内质网途径:一般认为,肝细胞凋亡主要有胞膜上的死亡受体途径(外源性途径)和胞质内的线粒体途径(内源性途径),内质网的凋亡信号途径往往归并于线粒体途径^[15,28]。近有学者发现,内质网应激亦在肝细胞发生凋亡中占重要作用,是独立的第3条凋亡信号途径^[29-30]。其信号转导涉及非折叠蛋白反应以及内质网内钙失衡,使Caspase-12活化,诱导GRP78/Bip, GRP94, GADD34, GADD45A, CHOP等分子伴侣产生增加,继而激活非细胞色素C依赖的Caspase-9,引起Caspase级联反应诱导凋亡^[31-32]。

2 细胞凋亡与NAFLD

2.1 NAFLD发病机制 NAFLD是一类与代谢相

关的肝脏疾病谱, 脂肪变性常见因素包括肥胖症、糖尿病、高脂血症. 尽管这些因素在NAFLD起到重要作用, 但NAFLD的发病及进展至NASH的机制尚未完全阐明, 目前广泛接受的观点是Day和James提出的“二次打击”学说^[33]. 第一次打击指各种原因如肥胖、胰岛素抵抗引起的肝脏脂肪蓄积和肝脂肪变性. 脂肪分解产生游离脂肪酸(free fatty acids, FFA), 促进肝内FFA的摄取与合成; 当过量的FFA超出肝脏通过线粒体氧化反应及极低密度脂蛋白(VLDL)形式排放入血的代谢能力时, 将导致肝细胞脂肪变性, 使肝脏对炎症反应和各种损伤因素的敏感性增高^[34-35]. 近来研究表明^[36-37], FFA的脂毒性能诱导JNK依赖线粒体途径和TNF- α 与蛋白酶B介导溶酶体途径导致肝细胞脂性凋亡, 产生氧化应激、炎症和纤维化反应. 第二次打击主要为氧化应激导致的脂质过氧化损伤及其异常细胞因子的作用致肝脏炎症和纤维化^[38]. 反应性氧化物(reactive oxidative species, ROS)引起脂质过氧化, 损伤肝细胞膜和线粒体功能, 激活Fas/FasL系统, Bcl-2家族, 进一步引起Caspase家族成员Caspase-8活化, 进而活化下游的Caspase-3等级联反应导致肝细胞凋亡. 脂肪变性的肝细胞对肠源性内毒素的清除能力降低, 内毒素刺激脂肪产生TNF- α 、IL-6等炎症细胞因子, 活化中性粒细胞启动炎症反应发生^[39-40]. 肝细胞凋亡后, 肝星状细胞(hepatic stellate cell, HSC)与枯否细胞(kupffer cell, KC)吞噬凋亡小体而活化, 释放大量的细胞因子, 可进一步作用于HSC, 促使其活化、增殖、转型为肌成纤维母细胞分泌细胞外基质(extracellular matrix, ECM)导致肝纤维化^[41]. 因此, 肝细胞凋亡直接、间接促进了炎症与纤维化^[42].

2.2 细胞凋亡与NASH及其进展

2.2.1 NASH: 是NAFLD进展的关键性的一种形式, 由1980年Ludwig *et al*^[43]发现在无固定饮酒史及其他肝病的患者身上出现类似酒精性脂肪性肝炎的肝损伤表现而首先命名. NASH在组织病理学上表现为: (1)肝细胞脂肪变性(2)肝实质炎症(主要是肝细胞气球样变和点状坏死, 肝腺泡三区和门管区混合性炎症细胞浸润, 可伴Mallory小体形成)(3)各种形式的肝纤维化^[44].

2.2.2 肝细胞凋亡与炎症直接相关: Feldstein *et al*^[45]对NASH患者肝组织活检标本应用TUNEL法检测肝细胞凋亡比单纯脂肪肝组或正常对照组显著增加, 并随NASH炎症与纤维化严重程度

增加而增加. Nan *et al*^[46]在小鼠NASH实验模型中也证实此观点. 首先, 在病理情况下, 不受调控的持续性的凋亡破坏肝细胞的完整性, 引起线粒体功能障碍导致肝脏炎症反应, 而当凋亡的程度超过吞噬细胞清除能力时, 产生凋亡小体能自发破裂释放其内含物引起组织损伤和炎症. Siebler *et al*^[47]报道将Jo-2(Fas拮抗剂抗体)注射入ob/ob小鼠体内激活Fas受体, 介导凋亡产生, 观察到鼠肝功能急剧下降并进展为重症肝坏死, 伴随大量炎症、坏死. Takehara *et al*^[48]证实肝细胞特异性Bcl-xL缺陷导致肝细胞持续性凋亡, 继而出现炎症与纤维化. 其次, 肝细胞凋亡趋化中性粒细胞, 将中性粒细胞募集到肝实质. TNFR-1与TNF- α 结合后, 作用于下游的核因子 κ B(nuclear factor- κ B, NF- κ B)和JNK激酶信号传导通路, 转录因子NF- κ B活化则能与其他活化的细胞因子如IL-6、IL-8及黏附分子形成炎症瀑布反应, 活化中性粒细胞引起肝脏炎症^[49]. Dorman *et al*^[50]报道内毒素血症引起肝损伤的鼠中, TNF- α 介导的肝细胞凋亡刺激CXC趋化因子诱导KC和巨噬细胞炎症蛋白-2(macrophage inflammatory protein-2, MIP-2)基因转录与蛋白合成, 趋化中性粒细胞从肝血窦转移入肝实质中. 最近的资料则显示死亡受体介导的信号除了导致凋亡并能直接造成肝脏炎症. 如FasL本身具有促炎症活动作用, Fas的促效剂能刺激肝趋化因子表达、中性粒细胞浸润导致炎症反应的发生. Altemeier *et al*^[51]研究证明Fas通过MyD88通路而不依赖于Caspase活性信号诱导巨噬细胞促炎症反应趋化因子表达, 直接促进中性粒细胞浸润与炎症反应.

2.2.3 肝细胞凋亡间接促进纤维化: Canbay *et al*^[52-53]研究表明肝星状细胞与枯否细胞能吞噬凋亡小体而活化, 释放大量的细胞因子如TGF- β 、TNF- α 、血小板衍生生长因子(platelet-derived growth factor receptor, PDGF)、IL-1、IL-6共同导致肝纤维化. TGF- β 能刺激原纤维胶原和纤维连接素基因转录的细胞因子, 能抑制胶原酶和蛋白酶的产生, 减少胶原的降解; 同时TGF- β 能通过减少HSC表面FasL基因和促凋亡因子p53的表达, 增加抑制凋亡因子NF- κ B、bcl-xL、p21WAF1的表达, 抑制活化的HSC的凋亡, 维持其持续活化^[54]. TNF- α 能促进HSC的增殖, 加强HSC的趋化性; 近来研究显示^[55-56], TNF- α 促进HSC表达间质金属蛋白酶(matrix metalloproteinase, MMP)参与纤维化过程. IL-6

■创新盘点

本文对着重对肝细胞凋亡的信号转导通路的分子机制进行阐述, 综述了病理性凋亡导致肝脏炎症、纤维化的机制及细胞凋亡应用于临床NAFLD诊断、治疗中研究成果与发展趋势.

■应用要点

本文阐述了肝细胞凋亡及相关调节因素在NAFLD发病机制中的深入研究结果,进一步阐明NAFLD的发病机制;为开发研制抑制肝细胞凋亡药物,从而减轻肝脏炎症与纤维化,阻断NAFLD进展提供有力的理论依据。

也可刺激HSC的增殖,并可诱导产生多种急性期蛋白,通过促进基质变性或与其黏附受体相互作用而促使ECM的沉积。PDGF通过自分泌和旁分泌作用有助于维持HSC的活化与增殖,并能与TGF- β 发挥协同作用。HSC的活化启动一系列信号级联反应,诱导各种与成纤维相关的基因表达并分泌大量细胞外基质在细胞间质过度沉积导致肝纤维化。肝纤维化则继续发展至肝硬化乃至肝癌^[57]。

3 细胞凋亡在临床NAFLD诊断与治疗中的应用

随着肝细胞凋亡在NAFLD发病进展机制的阐明,能给临床NAFLD患者的诊断、治疗及预后评估带来新的契机。Wieckowska *et al*^[58]在可疑NAFLD患者血清中通过原位免疫组化和ELISA检测由肝细胞凋亡Caspase-3产生细胞角蛋白-18片段(CK-18)在NASH与单纯脂肪肝或正常者相比显著升高,其诊断NASH的特异性为99.9%,敏感度为85.7%与同时做肝活检判断肝组织学改变一致。肝细胞凋亡定量指标Caspase活性作为一项非侵袭性的生物标记是NASH独立而有力的预测指标,有望用来判断NAFLD患者的严重程度。Manco *et al*^[59]学者检测NAFLD患儿的血清TNF- α 和瘦素水平,以及肝组织学损伤程度。结果显示, TNF- α 水平与肝脏病变程度密切相关。单独检测血清TNF- α 以及联合瘦素均能准确预测NAFLD患儿是否发生NASH病变,提示可用血清TNF- α 水平作为NASH患儿的特异性实验室指标。Cazanave *et al*^[60]在小鼠爆发性肝炎模型中证实,肝脏高谷胱甘肽储备能减轻予Fas促效剂(Jo-2)诱导的肝细胞凋亡,减轻肝脏炎症与纤维化,并提出还原型谷胱甘肽的临床应用价值。Miyasou *et al*^[61]发现依达拉奉可调节线粒体Bcl-xL和Bax,阻止细胞色素C释放和Caspase-3活性;减轻Fas诱导急性肝功能衰竭的小鼠的肝细胞凋亡及肝损伤,提高其成活率。Baskin-Bey *et al*^[62]在对胆碱-甲硫氨酸缺乏饮食(methionine and choline deficient diet, MCD)致小鼠肝脂肪变性实验中,用组织蛋白酶B(cathepsinB)抑制剂明显减轻冷缺血/再灌注损伤致肝细胞凋亡与肝损害。Inoue *et al*^[63]在胆碱缺乏饮食(choline deficient diet, CD)致大鼠肝癌模型中早期阶段用PBN(phenyl butyl nitron)处理降低了Fas的表达,抑制凋亡驱动的促炎症反应,能对抗其引发的致癌作用,并认为CD作为一种致NASH模式,早期Fas表达可作为判断NASH进展的一项很好的

指标。张莉 *et al*在大鼠非酒精性脂肪性肝炎实验模型中用己酮可可碱(PTX)可抑制TNF- α 在肝脏中表达,从而改善肝脏酶学,减轻肝组织炎症损伤;并能降低细胞外基质I、III型胶原的合成,减轻NASH引起的肝纤维化,对实验性NASH具有治疗作用^[64-65]。李继强 *et al*^[66]在大鼠肝实质损伤性肝纤维化模型中发现血管紧张素转化酶抑制剂(依那普利)能通过调节**bax**、**bcl-2**基因表达,起到调控肝细胞凋亡,防治肝纤维化的作用。

4 结论

肝细胞凋亡是连接肝损伤与炎症、纤维化的纽带与NAFLD的发生进展密切相关,但具体的机制及调节因素有待进一步研究阐明。随着对NAFLD中肝细胞凋亡的深入研究,能够进一步探明NAFLD的发病机制,为细胞凋亡运用于NAFLD的诊治提供有力的理论依据,给临床NAFLD的诊断、治疗、及预后判定开辟一条新的途径。

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■名词解释

内质网应激: 由于各种原因引起的内质网中出现错误折叠与未折叠蛋白在腔内聚集以及Ca²⁺平衡紊乱的状态, 称为内质网应激(ERS)。研究表明ERS是细胞的一种自我保护性机制, 适度的ERS可以恢复内质网及内环境的稳态、保持细胞活性, 但是过强或过长时间的ERS可以诱导一系列细胞因子的大量释放并最终导致细胞凋亡。ERS引起的细胞凋亡有一套自身的信号传递通路, 称为内质网相关性死亡(ERAD)途径。

■同行评价

本文条理清晰, 结构合理, 语言通顺, 资料完整, 具有较好的学术价值。

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• 消息 •

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