非药物性处理抑制缺血再灌注肝脏细胞凋亡的研究进展

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摘要 肝脏是人体最大的代谢器官, 肝脏任何损伤都可能导致全身稳定状态的改变。肝脏缺血再灌注损伤(hepatic ischemia reperfusion injury, HIRI)是临床常见的导致脂肪肝、非酒精性肝硬化和肝癌等疾病患者进行肝移植后肝功能受损的重要原因。细胞凋亡(apoptosis)是细胞自主、有序的死亡, 过程复杂, 参与因素多。凋亡可以清除肝内受损的细胞, 维持肝功能。故在HIRI中如何维持细胞凋亡的稳定状态成为保肝的关键。研究显示, 多种非药物性处理可平衡HIRI中细胞凋亡, 减少肝损伤。该文就近几年非药物性处理抑制缺血再灌注(ischemia reperfusion, IR)肝脏细胞凋亡作用的研究进展(如对凋亡诱导因素、凋亡信号转导通路、凋亡通路下游分子等)作一综述。

关键词 细胞凋亡; 非药物性处理; 缺血再灌注损伤; 肝脏

Progresses in Inhibitory Effect of Non-Drug Treatment on Liver Cells Apoptosis during Hepatic Ischemia-Reperfusion Injury

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Abstract Liver is the largest metabolic organ of human body, and its damage may lead to dyshomeostasis. Hepatic ischemia reperfusion injury (HIRI) is a crucial factors of liver dysfunction after liver transplantation for the patients suffered from fatty liver, non-alcoholic cirrhosis and liver cancer. As an autonomous and orderly death model, apoptosis can eliminate the damaged cells from the liver and improve its function. Hence, it is important to maintain the stable state of apoptosis in order to protect the liver from HIRI. Numerous studies have shown that non-drug treatments were helpful to promote apoptosis balance and reduce liver damage during HIRI. Here, this review summarized the progresses in the inhibitory effects of non-drug treatments on liver cells apoptosis during hepatic ischemia reperfusion injury, which involved the apoptosis inducing factors, its signal transduction pathway and its downstream molecules in recent years.

Keywords apoptosis; non-drug treatment; ischemia reperfusion injury; liver

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我国是肝脏疾病的高发国家, 在失血性休克、肝脏肿瘤切除及肝脏移植等疾病和手术中, 肝脏缺血再灌注损伤(hepatic ischemia reperfusion injury, HIRI)均参与其中。HIRI是多因子[1]介导的、肝细胞损伤不断加重的连续性病理过程。早期由它引起的器官衰竭达到10%, 并且容易引发急或慢性肝移植排斥[2]。鉴于损伤后续的严重并发症, 在肝脏损伤早期施行外源性干预十分重要。HIRI的转归有两种形式, 即坏死与凋亡[3], 其中以凋亡形式为主, 影响肝脏受损整个病理生理过程。本文就近年来有关非药物性处理对缺血再灌注肝细胞凋亡的调控机制作一综述。

1 HIRI与细胞凋亡

缺血基础上恢复血流后组织损伤反而加重, 甚至发生不可逆性损伤的现象称为缺血再灌注损伤(ischemia reperfusion injury, IRI)。再灌注时, 肝细胞损伤较单纯缺血明显加重, 血清丙氨酸氨基转移酶(alanine aminotransferase, ALT)、天冬氨酸氨基转移酶(aspartate aminotransferase, AST)活性明显升高。肝脏热IRI有明显的阶段分期。再灌注后5 h内称为再灌注早期, 以氧化应激和释放活性氧类(reactive oxygen species, ROS)直接损伤肝脏细胞为主; 再灌注后6~48 h称为HIRI晚期, 是中性白细胞聚集介导的炎症紊乱过程, 同时也释放ROS损伤肝脏细胞。中性白细胞激活释放的弹性蛋白酶、组织蛋白酶G、肝素酶、胶原酶和水化酶都对肝脏细胞有直接损害作用[4]。

细胞凋亡(apoptosis)是细胞降解DNA和蛋白质, 分裂成凋亡小体, 被邻近的吞噬细胞吞噬而很快去除, 且不引起炎症反应的调节过程[5]。凋亡的确切机制虽尚未完全清楚, 但细胞凋亡过程可大致分为: 接受凋亡信号→凋亡调控分子间的相互作用→蛋白酶(Caspase)的活化→进入连续反应阶段[6]。

HIRI与肝脏细胞凋亡关系密切。Vivek等[7]建立大鼠常温HIRI模型, 将采集的标本进行HE染色、TUNEL免疫组化染色及电子显微镜观察, 结果发现, IR后肝细胞和肝窦状上皮细胞的死亡方式主要是细胞凋亡。Sasaki等[8]行鼠肝缺血60 min后再分别灌注3、6、24、48 h, 发现肝细胞凋亡现象主要出现在再灌注早期。Kuo等[9]观察临床肝移植术后的肝细胞凋亡情况, 证实细胞凋亡与IRI造成的生化学和病理学参数改变相平行。宋少伟等[10]发现, 肝脏热IRI时, 未缺血的肝叶在再灌注后也出现细胞凋亡现象, 推断肝脏发生IRI可诱发相应的凋亡分子和凋亡诱导分子释放, 导致正常肝细胞发生凋亡。

有研究报道, 单纯缺血和IR均可造成组织损伤, 共同表现是细胞坏死和凋亡; 不同的是, 单纯缺血所致的损伤以坏死为主, IR以凋亡为主, 原因之一与B淋巴细胞瘤-2蛋白质(B-cell lymphoma-2, Bcl-2)减少、Caspase-3大量激活有关[11]。在光镜下, 肝脏细胞表现出凋亡特征即细胞通过嗜酸性变发生固缩: 染色质致密、断裂, 核固缩; 胞体变小, 胞质变致密, 形成嗜酸性小体。肝脏细胞在电镜下表现为: 核固缩, 电子密度增高, 染色体密集于皱缩的核膜下, 核碎片和细胞器等成分被细胞膜包裹形成圆形的凋亡小体[12]。

2 非药物性处理

大量动物实验证明, 人为干预措施可通过多种途径, 如抑制肝脏细胞凋亡、抑制炎症、减少肝脏细胞自噬、促进肝脏细胞再生等减轻HIRI。人为干预措施包括药物性和非药物性处理。药物性处理是针对损伤机制利用某些活性物质直接或间接的药理作用来达到减轻缺血损伤的目的[13]。某些药物具有较大的毒副作用, 限制了其临床应用[14]。非药物性处理指采取药物制剂外的其他处理方式如非药物性制剂[63]、手术方式[15]和吸入或灌注气体等保护组织细胞, 减轻损伤。抗HIRI的非药物处理形式各异, 为了较系统有序地阐述非药物性处理及其主要机制, 本文根据细胞凋亡的过程和非药物性处理的三个作用阶段即凋亡诱导因素、凋亡信号转导通路、凋亡通路下游分子, 介绍目前较为成熟的非药物处理的相关研究进展。

3 非药物性处理抗IRI肝脏细胞凋亡作用

3.1 作用于凋亡诱导因素

凋亡诱导因素是凋亡过程的启动者, 刺激细胞发生一系列相应改变。细胞因子失衡如白细胞介素(interleukin, IL)、肿瘤坏死因子(tumor necrosis factor, TNF)和其他炎性因子等是最常见的凋亡诱导因素。Xiang等[16]利用氢气抑制炎性因子释放的作用, 采取肝移植术后气管插管吸入2%氢气发现, 氢气吸入组TNF-α、IL-6水平较对照组显著下降, 肝细胞凋亡减弱。低血压灌注[17]、营养补充剂(谷氨

酰胺+抗氧化剂)[18]以及缺血预处理已被证实在HIRI中可抑制炎症因子释放。多篇文献报道了关于HIRI小鼠输注间充质干细胞条件培养液(MSC-CM)的实验, 发现MSC-CM的系统输注可阻止细胞促炎因子的表达、抑制死亡通路的激活, 减轻HIRI[19-20]。除细胞因子失衡外, H_2O_2、射线等理化因素也可诱导凋亡。体外应用MSC-CM[21]处理H_2O_2诱导的肝细胞凋亡模型, 发现具有缓解效应, 可能与MSC-CM阻止H_2O_2穿过细胞膜与细胞内金属离子反应产生羟自由基, 引起ROS增多和线粒体功能障碍有关[22-23]。此外, 免疫因素如细胞毒T淋巴细胞、微生物及其毒素亦是诱导因素。抑制凋亡诱导因素可从起始阶段减轻HIRI, 对达到预期实验目的有重要意义。

3.2 作用于细胞凋亡信号转导通路

细胞凋亡具有主动性和信号依赖性, 外界刺激传入细胞, 启动胞内信号转导机制诱导细胞凋亡。现学者普遍认为, 细胞凋亡发生至少有三条通路参与, 即死亡受体通路、线粒体通路和内质网通路[24], 多种酶和基因是通路联系的枢纽。

3.2.1 *死亡受体通路* 死亡受体通路又称凋亡外部途经, 靶细胞表面的死亡受体与配体结合导致死亡结构域(death domain, DD)与连接蛋白Fas相关死亡域蛋白(Fas-associating protein with a novel death domain, FADD)的C-端的DD结合, 激活Caspase-8及下游的Caspase-3, 介导细胞凋亡[25]。目前, 死亡受体信号通路主要有三类: Fas(factor associated suicide)/FasL(Fas ligand)、肿瘤坏死因子相关凋亡诱导配体(TNF-related apoptosis-inducing ligan, TRAIL)和肿瘤坏死因子受体(tumor necrosis factor receptor, TNFR)信号转导通路[26]。

三条主要信号通路内含众多独立且连通的信号途径, 如JAK-STAT(Janus kinase-signal transducer and activator of transcription)通路、核因子-κB(nuclear factor-κB, NF-κB)通路等。以核心的NF-κB通路为例, NF-κB蛋白质是介导肝外部炎性因子刺激枯否细胞进而引发HIRI的效应分子, 阻断NF-κB通路的活化可减轻肝损伤[27]。在TNFR信号通路中, TNF的DD与TNFR结合后募集衔接蛋白TRADD、肿瘤坏死因子受体相关因子-2(tumour-necrosis factor receptor associated factor-2, TRAF-2)、凋亡抑制因子1(cellular inhibitor of apoptosis 1, cIAP1)和受体相互作用蛋白1(receptor-interacting protein 1, RIP1)。RIP1泛素化激活NF-κB抑制蛋白(inhibitor of NF-κB, IκB)激酶IKK, IKK将使NF-κB抑制蛋白IκB发生磷酸化, 而后NF-κB解离进入细胞核, 转录抗凋亡基因*cIap-1*、*cIap-2*等[28], MAPK通路和JNK通路参与这一过程。激活NF-κB通路的同时引起Fas相关死亡区域蛋白样IL-1β转化酶抑制蛋白(FADD-like intedeukin-1-β converting enzyme inhibitory protein, FLIP)表达下降, 导致其抑制Caspase-8活化作用减弱, 此时, NF-κB通路发挥促凋亡作用[29]。在细胞凋亡方面, NF-κB通路究竟发挥抑制作用还是促进作用? 张聪[30]认为, NF-κB通路所发挥的作用取决于刺激因素和细胞类型。Cheng等[31]将NEMO结合域(NEMO-bonding domain, NBD)肽预处理70%肝移植的小鼠, 分析处理后小鼠的ALT、TNF-α、IKK复合物磷酸化水平和NF-κB转录活性, 发现实验组肝功能明显改善, 证实NBD肽预处理可减轻HIRI, 其机制可能为下调TNF-α水平, 减少与死亡受体TNFR-2结合的信号分子, 阻断NF-κB信号通路。Chen等[32]利用5-脱氧-Δ(12,14)-前列腺素J2(15d-PGJ2)预处理成功达到肝保护目的。这种效应可能依赖减少枯否细胞活化和激活人类NF-E2相关因子2(nuclear factor E2-related factor 2, Nrf2)途径。胞内Nrf2通路激活后, Nrf2与胞质结合蛋白Keap1(Kelch-like ECH-associating protein 1)解离, 进入细胞核与小Maf和Jun二聚体相互作用, 促进下游抗氧化基因转录, 抑制Caspase-3的表达[33]。Xiao等[34]和Li等[35]分别证明了低温预处理和预吸入高浓度氢气都可作用于磷脂酰肌醇3激酶(phosphatidylinositol 3-kinase, PI3K)/蛋白激酶B(protein kinase B, PKB, 也称为Akt)/哺乳动物雷帕霉素靶蛋白(mammalian target of rapamycin,mTOR)信号转导通路保护肝功能, 主要机制[36]包括: 抑制FKHR(forkhead in rhabdomyosarcoma)、NF-κB和YAP(Yes-associated protein, Yes相关蛋白), 促进环磷腺苷效应元件结合蛋白(cAMP response element binding protein, CREB)和鼠双微基因2(murine double mimute 2, Mdm2)等转录因子活性, 直接抑制Bad和Caspase-9磷酸化。李正天[37]给予小鼠2 h的氙气预处理(75%氙气+25%氧气), 结果显示, 肝脏缺氧诱导因子-1α(hypoxia inducible factor-1α, HIF-1α)、磷酸化Akt以及下游靶基因的表达明显升高、肝细胞损伤明显减轻, 再次证实PI3K/Akt及依赖于PI3K/Akt的HIF-1α通路的激活可介导肝保护作用。

3.2.2 线粒体通路 线粒体通路是细胞凋亡的内在途径, 已知由线粒体改变引起细胞凋亡有三种机制: (1)电子传递、氧化磷酸化和ATP产生的破坏; (2)释放激发Caspase家族的蛋白质细胞色素c(cytochrome C, Cyt c); (3)改变细胞氧化还原潜能[38]。马洪明[39]提出, 细胞内核苷酸是天然的凋亡小体抑制物, 是细胞凋亡的分子制动器。故凋亡程序的启动需释放大量的Cyt c。B细胞淋巴瘤/白血病-2(B cell lymphoma/leukaemia-2, Bcl-2)、Bcl-x(B-cell lymphoma-x)、Bcl-w(B-cell lymphoma-w)等Bcl-2凋亡抑制蛋白质可抑制Cyt c释放, 抑制超氧阴离子产生[40], 还可调节胞内钙离子浓度从而调控凋亡[41]。*bcl-2*是指B细胞淋巴瘤/白血病-2(B cell lymphoma/leukaemia-2), 在滤泡状B细胞淋巴瘤中发现, 与线虫*ced-9*(ced cell death abnormal-9)基因有23%的同源[42]。Bcl-2蛋白质家族是目前最受重视的调控细胞凋亡的蛋白质家族。

线粒体是细胞进行三羧酸循环、呼吸链电子传递和氧化磷酸化的场所, 为细胞活动提供能量。线粒体病变影响到细胞各成分的协调并危及细胞生命活动[43]。氧化代谢受限可导致线粒体功能障碍, 诱导细胞凋亡。

缺血预处理(ischemic preconditioning, IP)是目前抑制HIRI最常见处理方式之一。Rehman等[44]发现, IP可减少ALT、血清胆红素、坏死和凋亡标志物的58%增长水平。Jang等[45]采取IP、间歇性夹持以及Kong等[46]联合IP、丹酚酸-B预处理都可改善线粒体功能抑制小鼠HIRI。IP如何发挥保护HIRI作用? 正常状态下, 人体有一套完整的清除自由基系统, 维持自由基产生和清除的动态平衡。肝缺血时, 钙离子大量内流, 氧自由基生成增多, 超氧化物歧化酶(superoxide dismutase, SOD)被大量消耗[47], 限制了SOD清除氧自由基活性、维持细胞膜完整性和线粒体超微结构的作用[48], 导致体内自由基堆积诱导过氧化反应, 损伤细胞。多项IP实验结果中都伴有SOD水平升高现象, 表明IP护肝与其防止自由基堆积和线粒体功能障碍有关。

除经典的IP外, 还有许多非药物处理也作用于线粒体通路。一氧化氮(NO)是具有极强生物活性的气体分子, 可作为抗氧化剂降低超氧阴离子和自由基对肝脏细胞的损害, 降低肝毒性[49]。Lang等[50]通过临床随机对照试验评估了肝移植术前吸入NO(80 ppm, 4 h)的效果。实验发现, NO吸入患者住院时间和肝功能恢复时间的显著缩短与其血清硝酸盐、亚硝酸盐、亚硝基血红蛋白的浓度显著增加有关。循环的低亚微摩尔水平亚硝酸盐可抑制线粒体呼吸链, 减少活性氧产生[51]。血红素加氧酶-1(heme oxygenase-1, HO-1)参与抗氧化、抗炎症和抗细胞凋亡等过程[52], 并通过MAPK通路或PI3K-Akt通路进行表达[53]。Liu等[54]发现, 高压氧预处理HIRI大鼠可产生诱导型HO-1, 发挥抗凋亡效应。Ishima等[55]研究发现, S-硝基化人血清白蛋白(SNO-HSA)中NO成分在冷缺血期间发生细胞吸收, 且在冷缺血3 h内诱导HO-1, 减弱肝损伤, 结果还表明, SNO-HSA和UW溶液的组合可用于预防冷热两种类型的局部肝缺血损伤。Lin等[56]在IR前5天对治疗组口服从附子中分离的水溶性多糖FPS-1(160 mg/kg/天), 与模型组相比发现, FPS-1预处理逆转了Na^+-K^+-ATP酶和Ca^{2+}-ATP酶等生物化学参数及组织学改变, 与FPS-1预处理抗氧化和衰减坏死作用有关。Song等[57]利用门静脉灌流含降钙素基因相关肽(CGRP)的组氨酸、色氨酸-酮戊二酸(HTK)溶液(3 μg/10 g体质量), 证明CGRP可减轻由氧自由基和细胞凋亡引起的IRI。用含氢的氧缓冲液在37 ℃离体灌注装置中进行肝移植再灌注, 发现氢气在再灌注早期发挥线粒体保护功能, 抑制氧化应激和炎症级联反应, 减少肝脏冷保存后的再灌注损伤[58]。糖原合酶激酶3β(GSK3β)是氧化应激诱导细胞凋亡中的重要信号分子[59]。Liu等[60]发现, 慢性锂处理可减弱大鼠HIRI, 机制可能涉及抑制GSK3β活化, 减少MAPK活化, 抑制肝细胞凋亡及诱导自噬的能力。

线粒体功能障碍时线粒体通透性改变, 线粒体内膜电位下降, 线粒体通透性转换孔(permeability transition, PT)开放, 导致Cyt c释放到胞质中, 在dATP存在的条件下与凋亡相关因子-1(apoptotic protease activating factor-1, Apaf-1)结合成多聚体, 最终与Caspase-9结合形成凋亡小体, 或Caspase-9激活其他Caspase如Caspase-3, 引发凋亡级联反应。因此, 抑制线粒体Cyt c释放是减轻HIRI的重要手段。

Strifler等[61]在大鼠肝脏热IRI 60 min期间规范吸入含2.2%甲烷的常氧空气, 结果显示, Cyt c活性降低, ROS产生显著减少, 肝损伤减轻。Zhang等[62]设计NaHS预给药实验达到抑制电位改变和减弱损伤的效果。冷藏前灌注含前列腺素E1的含氧缓冲液[63], 同样可抑制Cyt c释放、阻止肝脏热IRI。Song

等[64]发现, 腺病毒心肌营养因子-1转移可改善IR后的存活率并且部分通过Akt、细胞外调节蛋白激酶(extracellular regulated protein kinases, ERK)和信号转导与转录活化因子-3(signal transducer and activator of transcription-3, STAT-3)存活信号通路介导。此外, 高糖饮食[65](标准实验室饮食+静注50%葡萄糖溶液1 mL/6 h)和缺氧预处理(8%氧环境, 90 min)[66]以及IP[67-68]都可增强Bcl-2的表达, 抑制Cyt c释放, 降低肝细胞凋亡指数。其中, Zhuang等[69]发现, IP可通过激活G蛋白偶联受体5(the G protein-coupled receptor 5, TGR5)上调Bcl-2表达, 但IP诱导抗凋亡分子表达的作用却被TGR5抑制, 具体原因尚不明确。

3.2.3 内质网通路 内质网是细胞内蛋白质合成并折叠的场所, 是细胞内Ca^{2+}的主要储存库, 腔内还含有凋亡相关蛋白质[如Caspase-12、B细胞受体相关蛋白31(B cell receptor associated protein 31, Bap-31)、Bcl-2]。内质网与细胞凋亡的联系表现在两个方面: (1)内质网内Ca^{2+}稳态的改变; (2)内质网应激反应[70]。内质网应激特异性激活Caspase-12, Caspase-12裂解Caspase-3等下游效应蛋白酶, 导致细胞凋亡。Zhang等[71]研究表明, 大鼠肝脏冷IR时细胞凋亡可能与内质网应激过度激活有关。

针对该通路的非药物性处理研究较少, 目前Mosbah等[72]实验发现, IGL-1溶液(institut georges lopez-1 solution, IGL-1 solution)可减少大鼠肝移植的内质网应激和细胞凋亡。乔亮[73]利用小鼠HIRI模型和小鼠胚胎肝细胞BNL CL.2缺氧/复氧模型, 发现再灌注过程中lncRNA-AK054386(一种长非编码RNA)的“海绵吸附”机制使有护肝作用的miR-199a-5p浓度迅速下降, 导致内质网应激持续存在, 最终造成肝损伤。该项研究提供了通过内质网途径减轻HIRI的新思路。

3.3 作用于凋亡通路下游分子

肝脏受到IR刺激时, 凋亡机制的启动和放大会造成IR直接损伤作用外的二次伤害[74]。以往人们较多关注凋亡过程中细胞核DNA被降解为寡核苷酸片段, 并认为片段是凋亡最重要的生化指标[75]。近年来, 研究焦点转移到凋亡过程中更早的一个环节, 即一系列在细胞中起关键作用的蛋白质被Caspase特异性水解的过程[76], 或DNA裂解酶(Dnase)裂解效应基因的过程。Caspase和Dnase破坏蛋白质的肽键或DNA的磷酸二酯键, 使蛋白质失活或基因变性, 最后吞噬细胞以胞吞形式吞噬凋亡细胞, 使细胞不可逆地走向死亡。

3.3.1 Caspase 人白介素-1β转换酶(interleukin-1β convert enzyme, ICE)是一种半胱氨酸蛋白酶, 能将IL-1β的前体在Asp116-Ala117处切断, 形成具有活性的IL-1β。现已在哺乳动物中发现14种结构相似、作用相同的ICE样蛋白酶, 统称为Caspase。凋亡的发生由凋亡信号活化启动性Caspase, 随后活化效应性Caspase, 效应性Caspase引起细胞凋亡: (1)激活凋亡特异性核酸酶, 即Caspase活化的DNA酶(caspase-activated Dnase, CAD); (2)降解细胞骨架蛋白; (3)裂解DNA修复的关键酶——多聚ADP核糖多聚酶(poly ADP-ribose polymerase, PARP)等[77]。

目前普遍认为, Caspase-3是细胞凋亡级联反应的必经之路, 因此下调Caspase-3可抑制细胞凋亡反应。蛋白激酶C(protein kinase C, PKC)介导氧化应激、炎症反应和细胞凋亡多个过程[78]。Tan等[79]证实, PKC参与CO_2预处理减轻大鼠HIRI的过程。CO_2预处理作为一种保护性酸化应激[80], 激活细胞膜上G蛋白偶联受体, 启动信号转导, 水解磷脂酶, 激活PKC, 使活化的Caspase-3表达下调。Chaves等[81]研究发现, 高压氧(hyperbari coxygen, HBO)治疗可使肝组织样本中Caspase-3裂解, 在实验中, 缺血早期应用HBO治疗HIRI效果良好, 再灌注后期HBO引起更严重的凋亡指数。大鼠小体积肝移植前转染腺病毒CT-1[64]可下调Caspase-3, 同时上调抗凋亡蛋白Bcl-2。Park等[82]运用腺病毒编码的人白细胞介素-10(human interleukin-10, *HIL-10*)基因或β-半乳糖苷酶(LacZ)通过肠系膜上静脉注入预期供体动物体内, 转导后48 h收获供体肝并在移植前存储于4 ℃乳酸林格氏液12 h。评估后发现, *HIL-10*基因转移改善了冷HIRI。细胞保护作用除可能涉及Caspase-3活性抑制外, 还与Cyt c释放减少、上调Bcl-2和HO-1分子有关。

3.3.2 Dnase 目前为止, 已发现20多种与凋亡相关的内切核酸酶, 可分为: DnaseI家族、DnaseII家族、Caspase依赖性内切核酸酶[83]。Caspase依赖性内切核酸酶由凋亡信号激活Caspase-3, 破坏ICAD(inhibitor of CAD)/CAD复合体, 使游离的CAD形成具有催化性的同型低聚物[84], 将DNA链切割成180 bp的整数倍片段, 使正常基因失去功能。DnaseI家族与DnaseII家族又称为Ca^{2+}、Mg^{2+}依赖性和非依

赖性内切核酸酶, 通过细胞凋亡诱导因子(apoptosis-inducing factor, AIF)激活CAD。

与细胞凋亡密切相关的热休克蛋白70(heat-shock protein 70, HSP70)可通过Caspase依赖性或非依赖性途径参与凋亡的内部及外部信号通路[85]。Lee等[86]研究发现, HSP70可抑制信号调控激酶(signal-regulated kinase, SEK)活性和JNK的磷酸化作用, 遏制JNK介导的凋亡通路。值得注意的是, HSP70与NF-κB通路类似, 具有促凋亡的双重作用。Zhang等[87]胃饲乙醇预处理大鼠的实验结果显示, HSP70升高, 最终表现为肝功能各项指标改善。

4 结语

HIRI是多细胞、多介质共同参与的反应过程, 其损伤效应远超机体的保护作用, 必须通过人为干预才能减少HIRI[88]。肝脏细胞凋亡是促使HIRI的因素之一, 非药物性处理通过多位点、多通路作用于肝细胞凋亡途径, 对缓解HIRI具有重要意义。此外, 许多非药物性处理、信号通路、胞内物质等具有抗凋亡和促凋亡的双重性, 如何找到有利于实验目的的平衡点并指导临床应用, 是目前的现实问题; 细胞凋亡中内质网通路为新兴方向, 针对该方面的非药物性处理有较大的进展空间。

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