【综述】

药物性肝损伤的肝细胞死亡方式及治疗药物研究进展

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摘 要： 药物性肝损伤（DILI）是临床常见的肝损伤类型，是严重的药物不良反应之一。细胞死亡是DILI的重要特征，药物可通过诱导内质网应激和激活死亡受体等方式激活凋亡通路，诱导肝细胞凋亡或坏死，诱发肝损伤。除凋亡和坏死外，DILI过程中还伴随着自噬、焦亡和铁死亡。自噬可以清除受损的蛋白质以及细胞器，是肝细胞存活的重要机制，但也可能诱导肝细胞死亡。焦亡和铁死亡是最近发现的细胞死亡方式，其在DILI中的作用尚未完全阐明。阻断肝细胞死亡通路，是治疗DILI的重要手段。水飞蓟素、柚皮素、人参皂苷等可以抑制肝细胞死亡通路，是DILI的潜在治疗药。针对不同细胞死亡方式的机制和特点，研究改善肝细胞死亡的药物对治疗DILI具有重要意义。总结了DILI中肝细胞死亡的机制，并论述了潜在的药物治疗，旨在为DILI的治疗提供参考。

关键词： 细胞死亡；药物性肝损伤；凋亡；坏死性凋亡；药物治疗

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Research advances of hepatocyte death and therapeutic drugs in drug-induced liver injury

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Abstract: Drug-induced liver injury (DILI) is a common clinical type of liver injury and serious adverse drug reaction. Cell death is an important feature of DILI. Drugs can activate the apoptosis pathway by inducing endoplasmic reticulum stress and activating death receptors, induce hepatocyte apoptosis or necrosis, and induce liver injury. In addition to apoptosis and necrosis, the process of DILI is also accompanied by autophagy, pyroptosis and ferroptosis. Autophagy can remove damaged proteins and organelles, and is an important mechanism for liver cell survival, but it may also induce liver cell death. Pyroptosis and ferroptosis are recently discovered cell death methods, and their role in DILI has not yet been fully elucidated. Blocking the hepatocyte death pathway is an important method for the treatment of DILI. Drugs such as silymarin, naringenin, and ginsenosides are potential therapeutic drugs for DILI because they can inhibit hepatocyte death pathways. Therefore, in view of the mechanisms and characteristics of different cell death modes, research on drugs to improve liver cell death is of great significance for the treatment of DILI. This article summarizes the mechanism and effects of liver cell death in DILI, and discusses potential therapeutic drugs, aiming to provide a reference for the treatment of DILI.

Key words: cell death; drug-induced liver injury; apoptosis; necroptosis; therapeutic drugs

药物性肝损伤（drug-induced liver injury，DILI）是指由药物本身和/或其代谢产物引起的肝损伤，或由其代谢产物引起的超敏反应而导致的免疫介导肝损伤。目前，全球已上市的药物中可能引起DILI

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的药物有1 100种以上，常见的药物包括抗结核药类、中药、抗肿瘤药物、抗生素类、解热镇痛剂类等[1]。DILI具有较高的发病率，已成为重要的世界医疗安全问题。目前临床上主要使用抗氧化剂*N*-乙酰半胱氨酸（*N*-acetylcysteine，NAC）治疗对乙酰氨基酚（acetaminophen，APAP）引起的急性肝衰竭（acute liver failure，ALF），使用异甘草酸镁治疗转氨酶明显升高的急性期肝细胞型或混合型DILI[2]。DILI包括直接肝损伤、特异质性肝损伤和间接肝损伤，发病机制复杂，迄今仍无特异性治疗方法[3]。因此，急需阐明DILI的发病机制，研发治疗性药物。

DILI的发病机制复杂，已经成为近年来的研究热点。Kaplowitz提出“上游、下游事件”假说，认为肝细胞损伤和防御失衡引起特异质肝损伤[4]。Russmann提出药物和（或）其代谢产物直接损伤肝细胞线粒体功能、引起肝细胞应激、激活免疫反应，引起肝细胞线粒体通透性改变，最终导致肝细胞凋亡和坏死，造成肝损伤[5]。可见细胞死亡是DILI的重要特征，是不同药物引起DILI的共同“终点”事件。在肝脏中，药物可通过诱导内质网应激（endoplasmic reticulum stress，ERS）和激活死亡受体（death receptor，DR）等方式诱导肝细胞凋亡或坏死[6]。除凋亡和坏死外，DILI的发病过程中也伴随着自噬、焦亡和铁死亡[6]。然而不同药物引起的肝细胞死亡方式不同，需要阻断的死亡通路也不同，因此急需要研究肝细胞死亡方式并寻找针对死亡通路的治疗性药物。本文主要论述DILI过程中的肝细胞死亡方式及其机制，以期寻找针对死亡通路的潜在治疗性药物，为预防和治疗DILI提供思路。

1 细胞凋亡

1.1 细胞凋亡通路

机体在外界毒素和（或）病原体侵入时，可以通过凋亡来清除受损细胞，维持肝脏的正常功能。细胞主要通过DR介导的外源性凋亡通路、线粒体介导的内源性凋亡通路、穿孔素/颗粒酶介导的凋亡通路及ERS介导的凋亡通路等途径发生凋亡[7]。外源性凋亡是由死亡配体和DR结合，通过胞质中的衔接蛋白募集凋亡信号分子，形成死亡诱导信号复合物，导致半胱氨酸天冬氨酸蛋白酶（cysteine aspartic proteases，Caspase）激活而诱发的[8]。内源性凋亡是由细胞色素C（cytochrome C，Cyt c）与凋亡蛋白酶激活因子-1（apoptosis protease activating factor-1，APAF-1）及Caspase-9形成凋亡复合体活化Caspase-3诱发的[9]。B淋巴细胞瘤-2蛋白（B-cell lymphoma-2，Bcl-2）通过维持线粒体的完整性从而抑制Cyt c的释放，抑制凋亡；而Bcl-2相关X蛋白（Bax）能促进Cyt c的释放，促进细胞凋亡[10]。蛋白激酶B（protein kinase B，Akt）通过抑制Caspase-9来抑制细胞凋亡[11]；线粒体融合蛋白2（mitofusin 2，Mfn 2）能够抑制磷脂酰肌醇3激酶（phosphatidyl inositol-3-kinase，PI3K）和Akt的磷酸化，促进细胞凋亡[12]。ERS诱发的细胞凋亡是由Ca^{2+}稳态发生改变、蛋白质出现未折叠和（或）错误折叠并在内质网蓄积而引发的[7]。ERS能激活肌醇依赖激酶（inositol requiring enzyme，IRE）、活化转运酶（activating transcription factor，ATF）6和双链RNA活化蛋白激酶样内质网激酶（protein kinase R-like ER kinase，PERK），进而激活内质网分子伴侣葡萄糖调节蛋白（glucose reguilated protein 78，GRP78）和C/EBP同源蛋白（C/EBP homology protein，CHOP）[13]，上调Bax表达和Cyt c的释放，活化Caspase-3、-8、-9，诱导细胞凋亡[14]；ERS也能激活c-Jun氨基末端激酶（cJun N-terminal kinasec，JNK）及p38丝裂原激活蛋白激酶（p38 mitogen activated protein kinase，p38）而促进细胞凋亡，JNK的激活导致线粒体内的活性氧（reactive oxygen species，ROS）增加，进而促进ERS和细胞凋亡[15]。

1.2 细胞凋亡与DILI

在肝脏中，药物通过引起肝细胞应激、ROS积累、内质网和线粒体应激造成细胞凋亡，最终造成DILI[16]。笔者课题组的研究结果显示，异烟肼6 mmol/L培养斑马鱼幼虫72 h，能促进肝线粒体ROS的生成，促进ERS，上调Bax、Caspase-3、-8、-9的表达，诱导肝损伤[17]。也有研究显示，用异烟肼20 mmol/L处理人肝癌细胞HepG2细胞、异烟肼40 mmol/L处理人肝正常细胞THLE-2细胞[18]、用异烟肼20 mmol/L处理人肝癌细胞Hep3B细胞[19]，均能上调Caspase-9，诱发凋亡；笔者课题组的研究结果显示，吡嗪酰胺5 mmol/L培养斑马鱼幼虫72 h，可降低过氧化物酶体增殖物激活受体（peroxisome proliferator-activated receptor，PPAR）α的表达水平，下调Bcl-2，上调Bax、Capspase-3、-9的表达水平，引起严重的氧化应激和肝损伤[20]。ig给予大鼠吡嗪酰胺2 g/kg可通过激活PERK-ATF4-CHOP信号通路诱导肝损伤[21]。利福平200 μmol/L处理人正常肝细胞L02细胞可以激活PERK-ATF4-CHOP信号通路，引起ERS，诱导凋亡[22]。给小鼠ig异烟肼50 mg/kg和ig利福平100 mg/kg可导致肝氧化应激，线粒体

通透性转变，导致脂肪变性和肝细胞凋亡[23]。抗肿瘤药物酪氨酸激酶抑制剂普纳替尼10 μmol/L、瑞戈非尼5 μmol/L和索拉非尼10 μmol/L处理HepG2细胞，可抑制细胞呼吸链复合物的活性，促进ROS的产生和Cyt c释放，导致细胞凋亡[24]。

中草药也能通过诱导肝细胞凋亡造成DILI。吡咯里西啶生物碱20 μmol/L处理肝原代细胞，可增加动力相关蛋白1（dynamin-related protein 1，Drp1）的水平，诱导JNK易位和激活，激活Caspase-3诱发肝细胞损伤[25]。柴胡皂苷d 2 μmol/L处理L02细胞，可上调自杀相关因子（factors associated suicide，Fas）表达，促进Cyt c释放，上调Bax、Caspase-3的表达，通过内源性和外源性途径诱发肝细胞损伤[26]。用12 μmol/L重楼皂苷VI处理人肝癌细胞HepaRG细胞[27]、40 μmol/L芦荟大黄素处理人正常肝细胞HL-7702[28]，可通过促进ROS的产生和线粒体膜电位去极化，激活Fas，Caspase-3、-8、-9，诱导肝细胞凋亡。用甘遂提取物8 μg/mL处理L02细胞，可上调APAF-1表达，下调Bcl-2/Bax比例，通过内源性途径诱导肝细胞损伤[29]；补骨脂甲素20 μmol/L处理HepG2细胞，可诱导ERS，通过Mfn2-Akt途径引起细胞凋亡[30]。给大鼠ip雷公藤甲素2 mg/kg，能上调Caspase-3表达，诱导肝细胞凋亡和坏死[31]。笔者所在课题组的研究显示，雷公藤甲素25 nmol/L处理L02细胞，可诱导Drp1易位，促进线粒体去极化，增加ROS，促进Cyt c的释放和Caspase-3活化，诱导L02细胞凋亡和大鼠肝损伤[32]。

1.3 潜在治疗性药物

研究发现，ig给予小鼠柚皮素100 mg/kg预处理，可以通过抑制氧化应激，上调Bcl-2表达，抑制Bax表达，抑制细胞凋亡来减轻ig异烟肼100 mg/kg和ig利福平100 mg/kg诱导的肝损伤[33]。给大鼠ig水飞蓟素200 mg/kg预处理7 d可抑制Caspase-3表达、下调Bax/Bcl-2的比例发挥抗凋亡作用，改善雷公藤甲素（2 mg/kg，ip）诱导的急性肝损伤[31]。ig给予小鼠黑参300 mg/kg[34]、人参皂苷300 mg/kg[35]预处理7 d能改善对APAP（250 mg/kg，ip）引起的氧化应激，上调Bcl-2/Bax比例，来缓解APAP引起的小鼠肝损伤。ig给予大鼠18β-甘草次酸300 mg/kg[36]、小檗碱25 mg/kg[37]预处理，通过上调大鼠转录因子-E2相关因子2（nuclear factor erythroid-2 related factor 2，Nrf2）和PPARγ信号通路，抑制氧化应激和细胞凋亡，保护肝脏免受甲氨蝶呤（20 mg/kg，ip）诱导的肝损伤。ig给予大鼠绿原酸（100 mg/kg）预处理，可抑制氧化应激和Caspases-3、-9介导的细胞凋亡，改善甲氨蝶呤（20 mg/kg，ip）诱导的肝损伤[38]。给大鼠ip氨溴索70 mg/kg可抑制大鼠JNK的磷酸化，抑制caspase-3的表达，改善顺铂（10 mg/kg，ip）所致的肝损伤[39]；给大鼠ig橘皮素100 mg/kg可抑制JNK和p38的表达，增加Bcl-2、下调Bax表达来改善顺铂（7.5 mg/kg，ip）所致的肝损伤[40]。给小鼠ig桔梗皂苷30 mg/kg预处理可增加腺苷酸活化蛋白激酶（AMP-activated protein kinase，AMPK）、PI3K和Akt的磷酸化水平，降低Bax、Caspase-3、-9的表达来减弱APAP（250 mg/kg，ip）诱导的凋亡[41]。给小鼠ig桔梗皂苷D（10 mg/kg）预处理可抑制小鼠JNK、p38磷酸化，抑制Bax的表达、上调Bcl-2的表达来减弱APAP（300 mg/kg，ip）诱导的小鼠肝毒性[42]。这些药物可以抑制细胞凋亡，可能成为临床上治疗DILI的潜在药物。

2 坏死性凋亡

坏死性凋亡是在细胞缺乏半胱氨酸天冬氨酸蛋白酶的情况下，由受体介导的Caspase独立的程序性细胞死亡途径[43]。在Caspase-8被抑制的情况下，相互作用蛋白激酶1（receptor interacting serine/threonine protein kinase 1，RIPK1）通过RIP同源相互作用基序（RIP homotypic interaction motifs，RHIM）与相互作用蛋白激酶3（receptor interacting serine/threonine protein kinase 3，RIPK3）结合，RIPK3随后招募底物混合谱系激酶样蛋白（mixed lineage kinase domain like pseudokinase，MLKL）并形成坏死小体（necrosome），破坏细胞膜完整性，导致坏死性凋亡的发生[44]。

APAP（10 mmol/L）可诱导人肝癌细胞HepaRG细胞释放高迁移率族蛋白1（high-mobility group box1，HMGB1），通过Toll样受体（toll-like receptors，TLR）4-β干扰素TIR结构域衔接蛋白（TIR-domain-containing adapter-inducing interferon-β，TRIF）-RIPK3途径诱导邻近肝细胞坏死[45]。ip给予小鼠APAP 500 mg/kg可增加小鼠肝脏中RIPK1和RIPK3的表达水平，诱导肝细胞坏死性凋亡，敲除RIPK3可以改善APAP诱导的肝损伤[46]；敲低RIPK1可以抑制Drp1易位，抑制JNK的活化和易位，对APAP诱导的肝损伤具有显著的保护作用[47]。小鼠ip给予0.125 mg RIPK1抑制剂（necrostain-1，Nec-1）抑制RIPK1活性可以减弱APAP（300 mg/kg，ip）诱导的肝RIPK3的上调，抑制JNK磷酸化、Bax易位和凋亡诱导因子（apoptosis inducing factor，

AIF）从线粒体到细胞核的易位，减轻APAP诱导的肝损伤[48]。

抑制肝细胞的坏死性凋亡是改善DILI的有效途径。研究发现，ig给予小鼠APAP 300 mg/kg 1 h后ig给予木蝴蝶素A-7-*O*-葡萄糖醛酸苷100 mg/kg，能够抑制APAP诱导的RIPK1和RIPK3的表达，抑制JNK相关的细胞凋亡和坏死性凋亡来改善APAP诱导的肝损伤，可能成为临床上治疗DILI的潜在药物[49]。

3 自噬

自噬过程中，细胞质和细胞器被双层膜结构吞噬，形成自噬小体，然后被运送到溶酶体降解和再循环[50]。自噬可以在低三磷酸腺苷（adenosine triphosphate，ATP）水平或去除受损的细胞器的情况下，循环再利用营养物质、清除受损的蛋白质以及细胞器、促进细胞存活和抵御外界不良刺激[51]。自噬体的形成和成熟受多种自噬相关蛋白（autophagy-related protein，ATG蛋白）和信号通路的调节[51]。雷帕霉素靶蛋白复合物-1（mechanistic target of rapamycin complex 1，mTORC1）通过磷酸化UNC-51样激酶1（Unc-51 like autophagy activating kinase 1，ULK1）来抑制起始复合物的形成，在应激状态下，mTORC1对ULK1和ATG13的抑制作用减弱[52]，而AMPK可以通过磷酸化和激活ULK1，促进ULK1易位至线粒体，促进线粒体自噬[53]。生长因子和PI3K-Akt途径通过Bcl-2同源结构域蛋白（Bcl-2 homologous domain protein，Beclin1）和mTORC1途径抑制自噬[54]。

笔者所在课题组的研究结果显示，用雷公藤甲素50 nmol/L处理L02细胞，可上调Drp1的表达，促进ROS产生，抑制ATP生成，改变线粒体动力学，导致线粒体自噬和肝损伤[55]。然而，在肝损伤过程中，自噬对肝细胞也发挥着重要的保护作用。敲除ATG7造成自噬缺陷，会增加氨基半乳糖（*D*-galactosamine，*D*-GalN）/脂多糖（lipopolysaccharide，LPS）诱导的小鼠急性肝损伤[56]。而上调ATG5的表达，诱导自噬，可以减轻硫代乙酰胺造成的肝损伤[57]。给大鼠ig 80 mg/kg黄芪甲苷IV可通过诱导自噬，抑制核苷酸结合寡聚化结构域样受体家族pyrin结构域蛋白（NOD-LRR-and pyrin domain-containing protein，NLRP）3炎性体的活化改善肝脏的炎症反应，有效预防顺铂（15 mg/kg，ip）引起肝损伤[58]。给小鼠ip非诺贝特750 mg/kg可以激活自噬，改善APAP（500 mg/kg，ip）的肝毒性[59]；自噬还有助于清除肝细胞中对乙酰氨基酚蛋白加合物，减轻APAP诱导的肝损伤[60]。研究证明，ip给予小鼠APAP（400 mg/kg）1 h后ip紫檀蔗60 mg/kg可以上调ATG7的蛋白表达和抑制哺乳动物雷帕霉素靶蛋白（mechanistic target of rapamycin，mTOR）的磷酸化，通过增强自噬通量来预防APAP诱导的小鼠肝毒性[61]。给小鼠ip白细胞介素（IL）-22（1 mg/kg）预处理可显著促进AMPK磷酸化，增加肝自噬体，改善APAP（400 mg/kg，ip）诱导的肝坏死[62]。给小鼠ip氯丙嗪6 mg/kg可以通过增加的溶酶体数量和自噬通量来改善APAP（500 mg/kg，ip）引起的肝损伤[63]。表明自噬有可能成为治疗DILI的重要靶点。

4 细胞焦亡

细胞焦亡是炎症相关的程序性细胞死亡模式，是由Caspase-1或Caspase-4、-5、-11的激活，并切割执行蛋白gasdermin D（GSDMD），促进GSDMD转移到质膜并诱导细胞破裂而诱导细胞死亡[64]。经典的焦亡途径是由NLRP1、NLRP3、NOD样受体家族天冬氨酸特异性半胱氨酸蛋白酶激活募集结构域4（NLRC4）、黑色素瘤缺乏因子2（absent in melanoma 2，AIM2）和适配器蛋白（apoptosis-associated speck-like protein containing a CARD，ASC）以及pro-caspase-1形成炎性小体复合物，激活Caspase-1，诱导焦亡[65]。细胞焦亡在清除细胞内细菌方面起着至关重要的作用，但也可能导致自身炎症和自身免疫性疾病[66]。ip给予小鼠APAP 300 mg/kg能够激活NLRP3炎性小体，并诱导损伤[67]。给小鼠ip Nec-1 1.65 mg/kg可抑制RIPK1可以抑制Caspase-1激活和IL-1β的产生，改善ip APAP 500 mg/kg诱导的肝损伤[46]。给小鼠ip小檗碱5 mg/kg预处理可以通过抑制炎性体途径，抑制Caspase-1和IL-1β的表达来改善APAP（500 mg/kg，ip）引起的肝损伤[68]。给小鼠ip紫草素12.5 mg/kg预处理能够抑制NLRP3的表达，改善APAP（300 mg/kg，ip）诱导的肝损伤[67]。给大鼠ig黄芪甲苷IV 80 mg/kg可通过抑制NLRP3的表达，改善顺铂（15 mg/kg，ip）诱导的肝损伤[58]。表明焦亡有可能成为治疗DILI的重要靶点。

5 铁死亡

铁死亡是由于铁的脂质过氧化和ROS堆积造成的细胞死亡形式[44]。谷胱甘肽（glutathione，GSH）依赖性抗氧化防御系统的失活导致ROS累积过多，产生膜脂质过氧化反应，诱发铁死亡[69]。铁死亡参与肝脏疾病的多个病理过程。使用铁死亡

抑制剂ferrostatin-1（10 mg/kg，ip）显著抑制刀豆蛋白A（concanavalin A，ConA）诱导的诱导型一氧化氮合酶（inducible NOS，iNOS）水平的上调，改善ConA（20 mg/kg，iv）诱导的肝损伤[70]。APAP过量会导致高活性代谢产物NAPQI过量形成，耗竭GSH，使用Ferrostatin-1 1 μmol/L可以改善APAP 20 mmol/L引起的原代小鼠肝细胞损伤[71]。表明铁死亡有可能成为治疗DILI的重要靶点。

6 结语

DILI的发病机制是多因素的，年龄、性别、遗传因素等都会影响DILI的发生和发展。DILI一旦确诊，应及时停用肝损伤相关药物，并及早治疗。目前临床上主要使用NAC治疗APAP引起的ALF，异甘草酸镁、还原型谷胱甘肽、糖皮质激素、硫普罗宁、熊去氧胆酸等药物具有一定的保肝作用，但这些药物对DILI的确切疗效尚未完全阐明，还需深入探究其疗效和作用机制、掌握药物治疗的适应证。

细胞死亡是不同药物引起DILI的共同“终点”事件，研究肝细胞死亡方式，寻求阻断死亡通路的方法已经成为研究的重点和热点。凋亡和坏死是DILI中最常见的细胞死亡形式，可以通过抑制DR、Caspase、RIPK1、RIPK3等途径抑制肝细胞凋亡和坏死性凋亡来缓解肝损伤。如柚皮素、人参皂苷、18β-甘草次酸、小檗碱、绿原酸等能通过抑制药物引起的氧化应激，抑制凋亡通路发挥肝保护作用，可进一步探究其肝保护的作用机制和疗效。

然而，细胞死亡途径之间相互干扰，抑制一个细胞死亡途径可能激活另一个细胞死亡途径，例如抑制Caspase-8可能会激活坏死性凋亡。因此，急需开发可共同抑制多种细胞死亡途径的药物。自噬可以降解受损的线粒体，维持线粒体的呼吸链功能，降低氧化应激来缓解肝损伤，黄芪甲苷IV、非诺贝特等可激活自噬，可进一步探究其肝保护作用。而细胞焦亡和铁死亡在DILI中的作用还知之甚少，还需进行更深入的研究。

DILI的发病机制复杂，目前对其机制研究较为匮乏，如药物引起的氧化应激、线粒体损伤、内质网应激、细胞死亡等在DILI中的作用尚未完全阐明。除此之外，DILI过程中通常伴随着多种细胞死亡方式，不同细胞死亡方式之间的干扰也为DILI的治疗带来了较大的挑战。因此，探究药物所致不同细胞死亡方式的机制和特点，仍是未来研究需要努力的方向。目前避免和减少DILI的发生，仍需临床医生和药师们合理用药，严格把关。

利益冲突 所有作者均声明不存在利益冲突

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