

铁死亡参与肝疾病研究进展

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[摘要] 肝脏作为机体新陈代谢的核心器官,深度调节体内各类营养物质的合成及代谢。铁死亡作为一种铁依赖性的脂质过氧化物积累引起的新型细胞程序性死亡方式,参与多种急慢性肝疾病的生理和病理进程。目前认为,在急性肝损伤、代谢相关脂肪性肝病、酒精性肝病、病毒性肝炎、自身免疫性肝炎等大部分肝疾病中,铁死亡可加速疾病进程;而在晚期肝纤维化和肝细胞癌中,铁死亡则延缓疾病进程。因此,靶向调控铁死亡能够有效预防并延缓急慢性肝疾病的发生发展。本文讨论了铁死亡在急性肝损伤、代谢相关脂肪性肝病、酒精性肝病、病毒性肝炎、自身免疫性肝炎、肝纤维化以及肝细胞癌等肝疾病中的最新研究进展,以期靶向铁死亡防治急慢性肝疾病提供新的理论依据。



[关键词] 铁死亡;铁代谢;肝疾病;铁死亡信号通路;综述

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Ferroptosis and liver diseases

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[Abstract] As the central organ of metabolism, the liver plays a pivotal role in the regulation of the synthesis and metabolism of various nutrients within the body. Ferroptosis, as a newly discovered type of programmed cell death caused by the accumulation of iron-

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dependent lipid peroxides, is involved in the physiological and pathological processes of a variety of acute and chronic liver diseases. Ferroptosis can accelerate the pathogenetic process of acute liver injury, metabolic associated fatty liver disease, alcoholic liver disease, viral hepatitis, and autoimmune hepatitis; while it can slower disease progression in advanced liver fibrosis and hepatocellular carcinoma. This suggests that targeted regulation of ferroptosis may impact the occurrence and development of various liver diseases. This article reviews the latest research progress of ferroptosis in various liver diseases, including acute liver injury, metabolic associated fatty liver disease, alcoholic liver disease, viral hepatitis, autoimmune hepatitis, liver fibrosis and hepatocellular carcinoma. It aims to provide insights for the prevention and treatment of acute and chronic liver diseases through targeting ferroptosis.

[**Key words**] Ferroptosis; Iron metabolism; Liver disease; Ferroptotic signaling pathway; Review

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[**缩略语**] 谷胱甘肽 (glutathione, GSH); 谷胱甘肽过氧化物酶 (glutathione peroxidase, GPX); 泛醌 (coenzyme Q, CoQ); 铁死亡抑制蛋白 (ferroptosis suppressor protein, FSP); 尼克酰胺腺嘌呤二核苷酸 (磷酸) [nicotinamide adenine dinucleotide (phosphate), NAD(P)H]; 鸟苷三磷酸环化水解酶 (guanosine triphosphate cyclohydrolase, GCH); 四氢生物蝶呤 (tetrahydrobiopterin, BH₄); 二氢叶酸还原酶 (dihydrofolate reductase, DHFR); 脱氢胆固醇还原酶 (dehydrocholesterol reductase, DHCR); 脱氢胆固醇 (dehydrocholesterol, DHC); *N*-乙酰-对苯醌亚胺 (*N*-acetyl-p-benzoquinone imine, NAPQI); Kelch样环氧氯丙烷相关蛋白 (Kelch-like ECH-associated protein, Keap); 核转录因子红系2相关因子 (nuclear factor-erythroid 2-related factor, Nrf); 沉默信息调节因子 (silence information regulator, SIRT); 血红素加氧酶 (heme oxygenase, HO); 微RNA (microRNA, miRNA, miR); 转铁蛋白受体 (transferrin receptor, TFR); 代谢相关脂肪性肝病 (metabolic associated fatty liver disease, MAFLD); 代谢相关脂肪性肝炎 (metabolic dysfunction-associated steatohepatitis, MASH); 肝细胞癌 (hepatocellular carcinoma, HCC); 法尼酯X受体 (farnesoid X receptor, FXR); 溶质载体家族 (solute carrier family, SLC); 酰基辅酶A合成酶长链家族 (acyl-CoA synthetase long-chain family, ACSL); 甲型肝炎病毒 (hepatitis A virus, HAV); 乙型肝炎病毒 (hepatitis B virus, HBV); 丙型肝炎病毒 (hepatitis C virus, HCV); 铁蛋白重链 (ferritin heavy chain, FTH); 成纤维细胞生长因子 (fibroblast growth factor, FGF); CDGSH含铁硫结构域蛋白 (CDGSH iron-sulfur domain-containing protein, Cisd); CC趋化因子配体 (chemokine CC-motif ligand, CCL); 可溶性*N*-乙基马来酰亚胺敏感因子附着蛋白受体 (soluble *N*-ethylmaleimide-sensitive factor attachment protein receptor, SNARE); 视网膜母细胞瘤 (retinoblastoma, Rb); NAD(P)H醌氧化还原酶 [NAD(P)H quinone oxidoreductase, NQO]

肝脏作为人体新陈代谢的中心站,参与各类营养物质如胆红素、脂质、氨基酸、胆固醇、蛋白质的代谢和药物代谢等。近年来,肝疾病(以下

简称肝病)患者逐年增加,每年导致200万例死亡,占有死亡人数的4%,已经成为全球范围疾病负担和死亡的主要原因之一^[1]。大量研究发

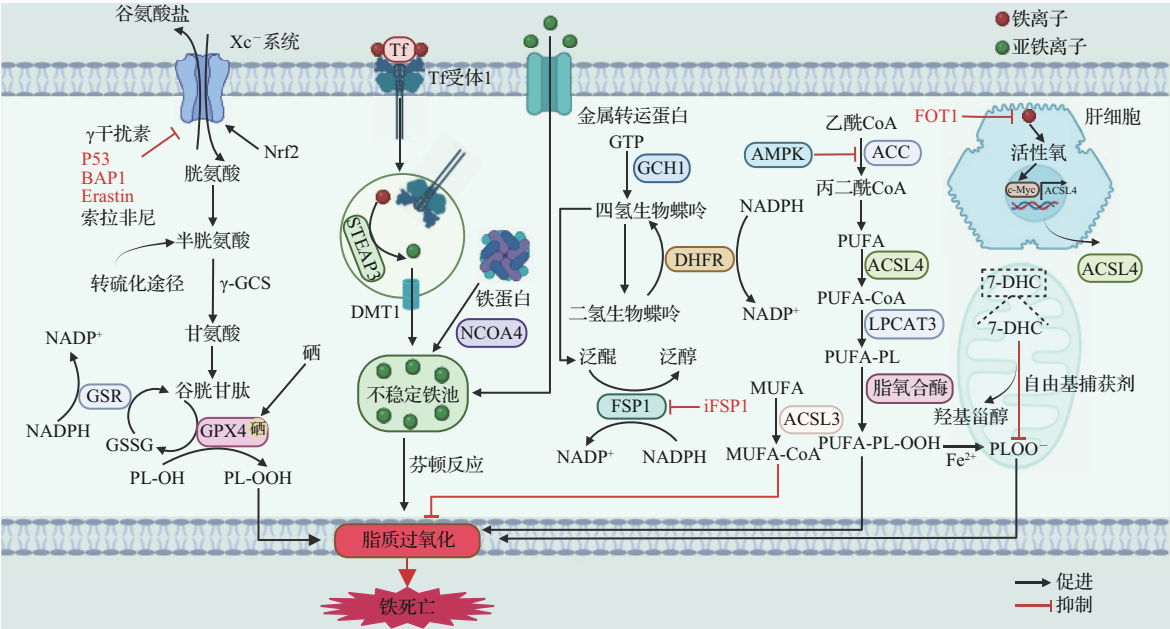
现,多种急慢性肝病的发展进程中均存在不同程度的铁代谢紊乱及脂质过氧化物积累等铁死亡现象,而铁死亡作为这些肝病的共同病理特征,在肝病的发生发展中起到重要的调控作用:一方面,肝细胞铁死亡能诱导大多数肝病进展,另一方面则可以改善肝纤维化、肝癌等晚期肝病的进程^[2-6]。

铁死亡作为一种铁依赖性脂质过氧化导致的细胞程序性死亡,其特点为细胞膜破裂、囊泡化、线粒体嵴减少、线粒体萎缩以及细胞核缺乏染色质凝集等形态学表现;细胞内铁离子水平升高、GSH耗竭以及生物膜内多不饱和脂肪酸脂质过氧化物的异常积累等生化方面表现。有学者利用小鼠模型揭示了 Mon1a 和铁转运蛋白是肝脏巨噬细胞和肝实质细胞铁离子调控的关键蛋白,为肝脏铁死亡研究奠定了理论基础^[7-9]。目前,铁死亡信

号通路及在肝病中调控的具体机制(包括 Xc⁻系统-GSH-GPX4 途径^[10]、CoQ10-FSP1-NAD(P)H 途径^[11]、GCH1-BH4-DHFR 途径^[12]、DHCR7/7-DHC 途径^[13]等)见图 1。基于此,本文归纳了目前铁死亡的调控机制,重点综述了铁死亡在多种急慢性肝病中的最新研究进展,以期铁死亡防治肝病提供参考和依据。

1 铁死亡参与药物性肝损伤、肝缺血/再灌注损伤等急性肝损伤

大多数急性肝损伤是由药物、酒精、缺血/再灌注损伤或病毒性肝炎引发的肝毒性所导致。其中,药物性肝损伤是造成急性肝损伤的主要原因。药物本身或个体差异可导致机体对药物的超敏反应或耐受性下降,进而造成肝脏损害,临床可表现为肝脏局部无症状、黄疸、肝炎样表现、胆汁淤积



铁死亡是一种铁依赖性的细胞程序性死亡方式,由细胞膜的脂质过氧化介导。铁离子经转铁蛋白受体进入细胞,并在体内中转化为亚铁离子,再通过 DMT1 从体内中释放。芬顿反应将亚铁离子转化为铁离子,后者通过激活脂氧合酶诱导脂质过氧化。Xc⁻系统促进谷胱甘肽合成,谷胱甘肽是 GPX4 的辅助因子,后者是抑制脂质过氧化的主要内源性机制。FSP1 通过脂质自由基水平上减少泛醇来防止脂质过氧化和相关铁死亡。GCH1 产生代谢物四氢生物蝶呤,后者参与介导脂质过氧化抑制。PUFA 以 ACSL4 和 LPCAT3 为催化剂,分两步合成 PUFA-PL,后者被脂氧合酶氧化生成 PUFA-PL-OOH,导致细胞铁死亡。7-DHC 是铁死亡的内源性抑制性因子,通过调控 7-DHC 水平来调节铁死亡敏感性。DMT1:二价金属离子转运体;GPX4:谷胱甘肽过氧化物酶;FSP1:铁死亡抑制蛋白;GTP:鸟苷三磷酸;GCH1:GTP 环化水解酶;PUFA:多不饱和脂肪酸;ACSL:酰基辅酶 A 合成酶长链家族;LPCAT:溶血磷脂酰胆碱酰基转移酶;PL:磷脂;PL-OOH:磷脂过氧化物;DHC:脱氢胆固醇;Nrf:核转录因子红系 2 相关因子;BAP:BRCA1 相关蛋白;GCS:谷氨酰半胱氨酸合成酶;NADP⁺:烟酰胺腺嘌呤二核苷酸磷酸(氧化态);NADPH:还原型烟酰胺腺嘌呤二核苷酸磷酸;GSR:谷胱甘肽二硫键还原酶;GSSG:氧化型谷胱甘肽;PL-OH:磷脂醇;Tf:转铁蛋白;STEAP:前列腺六跨膜上皮抗原;NCOA:核受体共激活因子;DHFR:二氢叶酸还原酶;MUFA:单不饱和脂肪酸;CoA:辅酶 A;AMPK:腺苷一磷酸活化的蛋白质激酶;ACC:乙酰 CoA 羧化酶。

图 1 铁死亡信号通路在肝病中的调控机制示意图

Figure 1 Schematic diagram of ferroptosis signaling pathway and its regulatory mechanism in liver diseases

性肝损伤、爆发性肝功能衰竭等^[14]。根据其发病机制的不同,药物性肝损伤可分为固有型和特异质型。对乙酰氨基酚是固有型药物性肝损伤的典型代表药物。当患者摄入对乙酰氨基酚时会产生具有高度活性和毒性的代谢产物NAPQI,正常状态下NAPQI与肝细胞内GSH结合形成无毒代谢物;而当对乙酰氨基酚摄入过量,肝细胞内GSH被耗竭,NAPQI在肝内大量堆积,从而导致内质网应激、线粒体氧化功能障碍、过氧亚硝酸盐及活性氧产生增多,最终导致肝细胞死亡甚至肝损伤^[15]。这与铁死亡的特征高度契合。研究表明,铁死亡抑制剂Fer-1、铁螯合剂去铁胺及维生素E处理均能有效抑制不同浓度对乙酰氨基酚诱导的肝损伤作用,且不影响GSH水平^[16-18]。(+) -Clausenamide在体内外均可以减轻对乙酰氨基酚或Erastin诱导的肝损伤,通过激活Keap1-Nrf2通路减轻对乙酰氨基酚诱导的肝细胞铁死亡^[19]。铁死亡抑制剂UAMC-3203和VDAC1寡聚化抑制剂VBIT-12可通过保护线粒体功能减轻对乙酰氨基酚诱导的药物性肝损伤小鼠模型中的铁死亡^[20-21]。乌司他丁作为治疗急性肝衰竭的有效药物,可通过SIRT1/Nrf2/HO-1通路减轻脂质过氧化物蓄积,抑制铁死亡,从而减轻对乙酰氨基酚诱导的急性肝损伤^[22]。虾青素通过激活Nrf2/HO-1通路增强自噬、抑制铁死亡,从而改善对乙酰氨基酚诱导的肝损伤^[23]。山柰酚通过激活Nrf2信号通路,降低活性氧积累,抑制铁死亡,从而逆转对乙酰氨基酚诱导的肝损伤^[24]。由此表明,铁死亡参与药物性肝损伤,可能作为对乙酰氨基酚诱导药物性肝损伤的治疗靶点。

肝脏缺血/再灌注损伤诱导的急性肝损伤会在肝移植、全身性休克、心力衰竭及败血症等多种疾病中发生,可诱导严重的肝损伤及不同形式的细胞死亡^[25]。研究发现,在脂肪性肝病缺血/再灌注损伤模型中铁死亡标志基因*IREB2*明显增加,使用miR-29a-3p可明显下调*IREB2*表达,抑制铁死亡,减轻肝缺血/再灌注损伤^[26]。在肝缺血/再灌注损伤和肾缺血/再灌注损伤模型中均可观察到丙二醛、亚铁离子、活性氧含量增加及GSH含量下降,而使用铁死亡抑制剂Liproxstatin-1可以有效减轻氧化应激导致的铁死亡,从而缓解缺血/再灌注损伤^[27]。使用铁死亡抑制剂Fer-1或 α -生育酚可明显降低脂质过氧化和铁死亡,改善肝缺血/再

灌注损伤^[28]。此外,高铁饮食引起铁过载可加重肝移植缺血/再灌注损伤,采用铁螯合剂去铁胺可以反转这一现象^[16]。泛素连接酶E3 HUWE1/MULE通过靶向TFR1负性调控铁死亡,从而减轻肝缺血/再灌注损伤^[29]。可见靶向铁死亡可能是治疗肝缺血/再灌注损伤的潜在靶点。

此外,双环醇作为我国自主研发用于治疗肝炎性损伤的一类化学药物,可以通过调节GPX4/Xc⁻系统活性抑制铁死亡,从而减轻急性肝损伤^[30]。温清引作为治疗各种炎症性疾病的经典中药配方,通过激活Nrf2通路抑制脓毒症肝损伤中的铁死亡,从而改善脓毒症肝损伤进程^[31]。

2 铁死亡促进代谢相关脂肪性肝病进程

MAFLD又名非酒精性脂肪肝病,是全球流行的主要肝病之一,严重威胁人类健康。目前,MAFLD逐渐取代病毒性肝炎成为我国最常见的肝病^[32]。MAFLD不仅可以引发肝病,还与心血管疾病、2型糖尿病、代谢综合征和恶性肿瘤等密切相关^[33]。MASH作为MAFLD中一种严重的疾病表现形式,可进一步发展为肝硬化和HCC。

研究表明,铁死亡能参与MAFLD进展,当肝细胞内FXR高表达时,敲除FXR基因或抑制FXR可增加肝细胞对铁死亡的易感性^[34]。在小鼠肝实质细胞中,特异性敲除TFR后给予高铁刺激可加重铁死亡诱导的肝纤维化,而铁死亡抑制剂Fer-1可逆转这一过程^[35]。最新研究发现,肝脏SLC7A11介导的非必需氨基酸代谢失衡会促进MASLD进展,补充丝氨酸或阻断铁死亡可能成为MASLD的治疗手段^[36]。此外,MAFLD中普遍存在的铁蓄积是诱发铁死亡的重要因素。通过对494例MAFLD患者的队列分析发现,相比单纯性脂肪肝患者,MASH患者中发生肝细胞铁蓄积的比例明显升高。同样,多种MASH小鼠模型均出现明显的肝细胞铁蓄积。进一步机制研究表明,肝细胞铁蓄积可通过上调c-Myc-ACSL4通路激活铁死亡,从而促进MASH发展^[37]。一些MAFLD临床标本和实验模型研究结果均显示,相比正常组或单纯性脂肪肝组,MASH组的血清铁蛋白水平明显升高,且血清铁蛋白水平与肝细胞铁蓄积明显相关^[38-39],提示MAFLD中血清铁蛋白水平与铁死亡有关。

由于铁死亡可促进MAFLD发展,靶向铁死

亡可能是缓解 MAFLD 的潜在治疗方法。如虾青素作为一种膳食补充剂,可通过减少氧化应激、炎症、胰岛素抵抗、脂质代谢及肝细胞纤维化预防 MAFLD 发生^[40]。铁死亡抑制剂 Trolox 或 Fer-1 可明显改善 MASH 肝损伤、脂质过氧化和免疫细胞浸润,逆转 MASH^[2]。最新研究发现,肝细胞铁蓄积通过 c-Myc-ACSL4 轴引发铁死亡,加速 MASH 疾病进展,新药筛选结果发现靶向该机制的新型铁螯合剂 FOT1 可有效防治 MASH 发生发展^[37]。随着研究的不断深入,铁死亡在 MAFLD 中的作用和潜在机制将更加清晰,靶向铁死亡治疗 MAFLD 的临床新药将会不断开发出来。

3 铁死亡是促进酒精性肝病的潜在因素

酒精性肝病指因长期过量饮酒导致的中毒性肝病,其疾病进展涉及脂肪肝、肝炎、肝纤维化和肝硬化等多个阶段,与肝细胞铁沉积的部位和范围密切相关^[41]。在酒精性肝病早期,亚铁离子主要沉积在肝实质细胞,通过芬顿反应增加脂质过氧化产物的产生、诱导细胞损伤,从而导致脂肪肝和肝纤维化^[42]。在酒精性肝病晚期,铁主要沉积于肝窦内皮细胞,不仅加重了脂多糖毒性,还促进内毒素血症和高细胞介质症发生发展,加速肝硬化进程^[43]。研究发现,酒精持续摄入会加速铁在肝脏的蓄积;触发内质网应激和炎症反应,上调铁调素,从而促进铁在肝脏巨噬细胞中的沉积;进一步增加肠道对铁的吸收,导致或加重酒精性肝病发生发展^[2]。

大量科学研究揭示铁死亡可能是酒精性肝病的潜在触发因素^[44]。研究表明,小鼠给予乙醇刺激后可出现明显铁死亡迹象,包括铁的过度累积、脂质过氧化以及铁死亡相关基因和炎症因子表达增加^[45]。过表达磷脂酸磷酸水解酶 1 会加速乙醇喂养小鼠肝脏中的铁积累,并引发脂质过氧化反应,导致 GSH 和甘油酸-3-磷酸脱氢酶水平下降,诱导铁死亡,加剧肝损伤^[46]。相比程序性坏死抑制剂 Nec-1,铁死亡抑制剂 Fer-1 在体内外可以明显改善酒精性肝病^[47]。另外,富马酸二甲酯可通过激活 Nrf2/GPX4 通路抑制铁死亡,从而改善酒精性肝病小鼠肝损伤^[48]。

综上所述,铁死亡在酒精性肝病发生和发展过程中发挥关键作用,针对靶向铁死亡的治疗策略可能会成为缓解酒精性肝病的重要手段。

4 铁死亡影响病毒性肝炎的发生

病毒性肝炎是指由 HAV、HBV、HCV 等多种肝炎病毒引起的以肝脏炎症和坏死病变为主的一组传染病^[49]。病毒性肝炎传染性强、传播途径广,其持续恶化会严重损伤患者肝脏,甚至导致肝癌^[50]。研究发现,感染 HAV 的肝细胞中线粒体膜电位下降及脂质过氧化现象^[51]。HBV/HCV 感染导致肝纤维化的组织中,铁调素及与纤维化相关指标发生改变,其中血清铁蛋白水平变化尤为重要,可以反映疾病的严重程度。此外,铁稳态失衡与 HBV/HCV 感染的发病率呈正相关^[52]。研究表明 HBV 感染可通过活性氧调节铁代谢,从而影响肝损伤进程^[53]。HCV 感染可通过诱导氧化应激抑制肝脏铁调素、上调二价金属转运蛋白 1,加剧肝脏铁蓄积,促进肝损伤;还可通过激活铁代谢相关基因(如 *FTH1*、*TFR1*、*GPX4*)诱发肝细胞铁死亡,促进 HCV 感染向肝细胞癌发展^[53]。另有研究发现,HCV 感染可诱导肝细胞发生铁过载,而 TFR1 作为重要的细胞铁转运蛋白,可通过调节 HCV 驱动的肝实质细胞和肝巨噬细胞铁代谢促进 HCV 复制和翻译^[51, 53]。这些研究揭示了肝细胞铁死亡与病毒性肝炎的发病机制紧密相关。

研究发现,艾曲波帕能通过铁螯合作用、抑制活性氧产生等方式抑制由 α 干扰素诱导的干扰素刺激基因表达,从而改善 HBV 引起的肝损伤^[54]。一些天然化合物如木黄素-7-O-葡萄糖苷、山竹果皮乙醇提取物等可通过抑制 HBV/HCV 复制和活性氧积累靶向铁死亡,从而减轻 HBV/HCV 导致的肝损伤^[55-56]。靶向铁死亡有望改善病毒性肝炎进展,但目前铁死亡治疗病毒性肝炎的临床药物研究仍较为不足,尚需进一步研发。

5 铁死亡参与自身免疫性肝炎

自身免疫性肝炎是一种由自身免疫系统异常激活引起的慢性肝脏炎症疾病,自体免疫系统错误攻击肝细胞,导致肝组织发生炎症和坏死,其病理过程包括肝细胞破坏、肝脏炎症坏死、肝纤维化乃至肝硬化^[57]。自身免疫性肝炎的临床表现包括高转氨酶、高免疫球蛋白,以及自身抗体阳性、淋巴细胞和浆细胞浸润。自身免疫性肝炎的发病机制复杂,其致病因素包括环境、遗传、表观遗传异常及其他因素驱动的炎症因子^[58]。

研究表明,在 *GPX4* 基因敲除的自身免疫性肝炎小鼠模型中,脂质过氧化产物丙二醛和亚铁离子在肝脏中聚集增多,从而加剧铁死亡^[59]。在刀豆蛋白 A 诱导的自身免疫性肝炎小鼠模型中,通过对差异表达的信使 RNA 进行通路富集分析发现,自身免疫性肝炎进展与铁死亡通路明显相关^[60];消耗 FGF4 会加重肝细胞脂质过氧化及铁积累,从而导致肝脏铁死亡,使用铁死亡抑制剂 Fer-1 可以逆转这种现象,且体内实验均发现非有丝分裂 rFGF4 可通过增加 Cisd3 水平激活 Nrf2/HO-1 信号通路,从而抑制肝细胞铁死亡^[61]。上述研究提示,针对铁死亡的治疗策略可能是自身免疫性肝炎治疗的新方向。

6 铁死亡双向影响肝纤维化的发生发展

肝纤维化是一种常见的慢性肝病过程,由多种诱因引起,其主要特征是肝组织内细胞外基质过度堆积,导致肝组织结构 and 功能受到持续性损害,最终可能发展为肝硬化或肝癌^[62]。大量研究发现,纤维化的肝脏中游离铁和脂质过氧化物明显增多,提示铁死亡可能参与肝纤维化^[63]。在肝硬化患者和肝硬化小鼠模型中观察到转铁蛋白水平明显下降,在特异性敲除转铁蛋白相关基因的小鼠模型中,小鼠血清铁含量明显减少,而肝组织中游离铁含量增加,并促使肝细胞发生铁死亡,从而引起肝纤维化;特异性敲除肝脏 *SLC39A14* 或使用铁死亡抑制剂 Fer-1 能明显减轻由高铁饮食或 CCL4 诱导的小鼠肝纤维化^[31]。rFGF21 作为一种新的铁死亡抑制因子,通过促进 HO-1 泛素化降解和激活 Nrf2 通路来抑制肝细胞铁死亡,从而改善肝纤维化^[64]。上述研究提示肝细胞铁死亡是导致肝纤维化的重要原因。

研究显示,肝星状细胞可以参与细胞外基质合成^[65],其活化是肝纤维化发展的核心事件。靶向抑制肝星状细胞活化可以改善肝纤维化。铁死亡也可以通过抑制肝星状细胞活化来改善肝纤维化。研究显示,抑制锌指蛋白 36 可提高 ELAVL1/HuR 表达水平,刺激肝星状细胞发生铁自噬,进一步触发肝星状细胞铁死亡,从而改善肝纤维化^[66-67];异甘草酸通过激活 HO-1 介导的肝星状细胞铁死亡改善肝纤维化^[68];蒿甲醚作为一种青蒿素的衍生物,通过抑制 SLC7A11 表达影响 GSH/GPX4,导致活性氧过量累积,进而触发肝星

状细胞铁死亡,改善肝纤维化^[69];青蒿琥酯通过激活细胞铁自噬来诱导肝星状细胞铁死亡,减缓肝星状细胞活化,改善肝纤维化^[70];多酚类化合物鞣花酸可以通过破坏 SNARE 复合物的生成,促进肝星状细胞对铁转运蛋白依赖性的铁死亡,有效改善 CCL4 诱导肝纤维化小鼠的肝损伤^[71]。

上述研究结果揭示了铁死亡在肝纤维化发展中的双重作用:既可以通过抑制肝细胞铁死亡阻止肝纤维化的进展,也可以通过促进肝星状细胞铁死亡改善肝纤维化。

7 铁死亡可抵抗肝细胞癌发展进程

HCC 作为慢性肝病患者中患病率最高的原发性肝癌,其发病机制复杂,主要由肝炎病毒及肝硬化导致^[72]。近年来,大量研究表明铁死亡可参与 HCC 发生发展^[73-78]。与正常肝组织比较,HCC 组织内部存在异常铁吸收、脂质代谢失调、RAS 致癌基因表达增加和铁水平升高,增加了 HCC 细胞铁死亡的敏感性^[73]。研究发现,索拉菲尼可通过抑制 SLC7A11 表达影响 GSH 合成及 GPX4 活性,从而诱导 HCC 铁死亡,延缓 HCC 发展进程^[74]。另有研究发现,与 Rb 蛋白正常表达的 HCC 荷瘤小鼠比较,Rb 蛋白低表达的 HCC 荷瘤小鼠经索拉菲尼治疗后其 HCC 细胞更容易发生铁死亡,HCC 进程也能得到缓解^[75]。Cisd1 是一种位于线粒体外膜的铁硫结构域蛋白,可对线粒体的铁代谢及氧化呼吸作用进行功能性调节,促进线粒体的铁摄取及脂质过氧化,从而诱发 HCC 细胞铁死亡,抑制 HCC 进展^[76]。Sun 等^[77]发现,激活 P62-Keap1-Nrf2 信号通路可通过上调铁代谢和活性氧代谢相关蛋白(如 NQO1、HO-1 和 FTH1)抵抗 Erastin、索拉菲尼诱导的 HCC 细胞铁死亡。与 Nrf2 对氧化应激反应的调节作用相似,Sigma-1 受体可促进 HCC 细胞对铁死亡的抵抗^[78]。可见铁死亡能参与 HCC 疾病进展,诱导 HCC 铁死亡发生可能是治疗 HCC 的可行策略。

8 结 语

肝脏作为代谢的中心器官,不仅是体内代谢的枢纽,也是铁死亡在多种急慢性肝病中发挥作用的场所。本文探讨了铁死亡在常见肝病中扮演的角色及其潜在分子调控机制。铁死亡调控在多种肝病的治疗中已显示出潜力,但人们对铁

死亡在肝病中作用机制的认识仍有待完善。因此,以铁死亡为靶点治疗肝病仍面临巨大挑战,深入研究铁死亡在肝病中的作用机制对全面认识和治疗疾病至关重要。另外,靶向铁死亡的药物也正在研发中,将为肝病的治疗提供更多机会。目前,大多数研究数据都是基于动物实验或细胞实验,未来需要更多基于人群的临床研究来开发治疗肝病的药物。

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医学伦理 研究不涉及人体或动物实验

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利益冲突 所有作者均声明不存在利益冲突

Conflict of Interests The authors declare that there is no conflict of interests

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参考文献(References)

- [1] DEVARBHAVI H, ASRANI S K, ARAB J P, et al. Global burden of liver disease: 2023 update[J]. **J Hepatol**, 2023, 79(2): 516-537.
- [2] CHEN J, LI X, GE C, et al. The multifaceted role of ferroptosis in liver disease[J]. **Cell Death Differ**, 2022, 29(3): 467-480.
- [3] JIA M, ZHANG H, QIN Q, et al. Ferroptosis as a new therapeutic opportunity for nonviral liver disease[J]. **Eur J Pharmacol**, 2021, 908: 174319.
- [4] DIXON S J, LEMBERG K M, LAMPRECHT M R, et al. Ferroptosis: an iron-dependent form of nonapoptotic cell death[J]. **Cell**, 2012, 149(5): 1060-1072.
- [5] MEHTA K J, FARNAUD S J, SHARP P A. Iron and liver fibrosis: mechanistic and clinical aspects[J]. **World J Gastroenterol**, 2019, 25(5): 521-538.
- [6] STOCKWELL B R. Ferroptosis turns 10: emerging mechanisms, physiological functions, and therapeutic applications[J]. **Cell**, 2022, 185(14): 2401-2421.
- [7] WANG F, PARADKAR P N, CUSTODIO A O, et al. Genetic variation in Mon1a affects protein trafficking and modifies macrophage iron loading in mice[J]. **Nat Genet**, 2007, 39(8): 1025-1032.
- [8] ZHANG Z, ZHANG F, AN P, et al. Ferroportin1 deficiency in mouse macrophages impairs iron homeostasis and inflammatory responses[J]. **Blood**, 2011, 118(7): 1912-1922.
- [9] ZHANG Z, ZHANG F, GUO X, et al. Ferroportin1 in hepatocytes and macrophages is required for the efficient mobilization of body iron stores in mice[J]. **Hepatology**, 2012, 56(3): 961-971.
- [10] JIANG X, STOCKWELL B R, CONRAD M. Ferroptosis: mechanisms, biology and role in disease[J]. **Nat Rev Mol Cell Biol**, 2021, 22(4): 266-282.
- [11] DOLL S, FREITAS F P, SHAH R, et al. FSP1 is a glutathione-independent ferroptosis suppressor[J]. **Nature**, 2019, 575(7784): 693-698.
- [12] KRAFT V, BEZJIAN C T, PFEIFFER S, et al. GTP cyclohydrolase 1/tetrahydrobiopterin counteract ferroptosis through lipid remodeling[J]. **ACS Cent Sci**, 2020, 6(1): 41-53.
- [13] LI Y, RAN Q, DUAN Q, et al. 7-Dehydrocholesterol dictates ferroptosis sensitivity[J]. **Nature**, 2024, 626(7998): 411-418.
- [14] CLOUSTON A D, GOUW A S H, TINIAKOS D, et al. Severe acute liver disease in adults: contemporary role of histopathology[J]. **Histopathology**, 2024, 85(4): 549-561.
- [15] BJÖRNSSON H K, BJÖRNSSON E S. Drug-induced liver injury: pathogenesis, epidemiology, clinical features, and practical management[J]. **Eur J Intern Med**, 2022, 97: 26-31.
- [16] ADELUSI O B, ETEMADI Y, AKAKPO J Y, et al. Effect of ferroptosis inhibitors in a murine model of acetaminophen-induced liver injury[J/OL]. **J Biochem Mol Toxicol**, 2024, 388(8): e23791.
- [17] ADELUSI O B, RAMACHANDRAN A, LEMASTERS J J, et al. The role of iron in lipid peroxidation and protein nitration during acetaminophen-induced liver injury in mice[J]. **Toxicol Appl Pharmacol**, 2022, 445: 116043.
- [18] JAESCHKE H, RAMACHANDRAN A. The role of oxidant stress in acetaminophen-induced liver injury [J]. **Curr Opin Toxicol**, 2020, 20-21: 9-14.
- [19] WANG M, LIU C Y, WANG T, et al. (+)-Clausenamide protects against drug-induced liver injury by inhibiting hepatocyte ferroptosis[J]. **Cell Death Dis**, 2020, 11(9): 781.
- [20] MA X, MCKEEN T, ZHANG J, et al. Role and mechanisms of mitophagy in liver diseases[J]. **Cells**, 2020, 9(4): 837.
- [21] NIU B, LEI X, XU Q, et al. Protecting mitochondria via inhibiting VDAC1 oligomerization alleviates ferroptosis in acetaminophen-induced acute liver injury[J]. **Cell Biol Toxicol**, 2022, 38(3): 505-530.
- [22] WANG C, LIU T, TONG Y, et al. Ulinastatin protects against acetaminophen-induced liver injury by allevi-

- ating ferroptosis via the SIRT1/NRF2/HO-1 pathway [J]. **Am J Transl Res**, 2021, 13(6): 6031-6042.
- [23] CAI X, HUA S, DENG J, et al. Astaxanthin activated the Nrf2/HO-1 pathway to enhance autophagy and inhibit ferroptosis, ameliorating acetaminophen-induced liver injury[J]. **ACS Appl Mater Interfaces**, 2022, 14(38): 42887-42903.
- [24] LI H, WENG Q, GONG S, et al. Kaempferol prevents acetaminophen-induced liver injury by suppressing hepatocyte ferroptosis via Nrf2 pathway activation[J]. **Food Funct**, 2023, 14(4): 1884-1896.
- [25] GEORGE J, LU Y, TSUCHISHIMA M, et al. Cellular and molecular mechanisms of hepatic ischemia-reperfusion injury: the role of oxidative stress and therapeutic approaches[J]. **Redox Biol**, 2024, 75: 103258.
- [26] LI X, WU L, TIAN X, et al. miR-29a-3p in exosomes from heme oxygenase-1 modified bone marrow mesenchymal stem cells alleviates steatotic liver ischemia-reperfusion injury in rats by suppressing ferroptosis via iron responsive element binding protein 2[J]. **Oxid Med Cell Longev**, 2022, 2022: 6520789.
- [27] LI X, MA N, XU J, et al. Targeting ferroptosis: pathological mechanism and treatment of ischemia-reperfusion injury[J]. **Oxid Med Cell Longev**, 2021, 2021: 1587922.
- [28] YAMADA N, KARASAWA T, WAKIYA T, et al. Iron overload as a risk factor for hepatic ischemia-reperfusion injury in liver transplantation: potential role of ferroptosis[J]. **Am J Transplant**, 2020, 20(6): 1606-1618.
- [29] WU Y, JIAO H, YUE Y, et al. Ubiquitin ligase E3 HUWE1/MULE targets transferrin receptor for degradation and suppresses ferroptosis in acute liver injury [J]. **Cell Death Differ**, 2022, 29(9): 1705-1718.
- [30] ZHAO T, FAN X, DENG Y, et al. Bicyclol mitigates acute liver injury via inhibition of ferroptosis by modulating GPx4/Xc⁻ system activity[J]. **J Hepatol**, 2020, 73: S25.
- [31] XIE L, ZHOU C, WU Y, et al. Wenqingyin suppresses ferroptosis in the pathogenesis of sepsis-induced liver injury by activating the Nrf2-mediated signaling pathway [J]. **Phytomedicine**, 2023, 114: 154748.
- [32] YOUNOSSI Z M. Non-alcoholic fatty liver disease—a global public health perspective[J]. **J Hepatol**, 2019, 70(3): 531-544.
- [33] ZHOU J, ZHOU F, WANG W, et al. Epidemiological features of NAFLD from 1999 to 2018 in China[J]. **Hepatology**, 2020, 71(5): 1851-1864.
- [34] PATEL K, HARRISON S A, ELKHASHAB M, et al. Cilofexor, a nonsteroidal FXR agonist, in patients with noncirrhotic NASH: a phase 2 randomized controlled Trial[J]. **Hepatology**, 2020, 72(1): 58-71.
- [35] YU Y, JIANG L, WANG H, et al. Hepatic transferrin plays a role in systemic iron homeostasis and liver ferroptosis[J]. **Blood**, 2020, 136(6): 726-739.
- [36] SHEN J, XIE E, SHEN S, et al. Essentiality of SLC7A11-mediated nonessential amino acids in MASLD[J]. **Sci Bull (Beijing)**, 2024, 69(23): 3700-3716.
- [37] TAO L, YANG X, GE C, et al. Integrative clinical and preclinical studies identify FerroTerminator1 as a potent therapeutic drug for MASH[J]. **Cell Metab**, 2024, 36(10): 2190-2206.e5.
- [38] ZHANG J, WANG Y, FAN M, et al. Reactive oxygen species regulation by NCF1 governs ferroptosis susceptibility of Kupffer cells to MASH[J]. **Cell Metab**, 2024, 36(8): 1745-1763.e6.
- [39] CORRADINI E, BUZZETTI E, DONGIOVANNI P, et al. Ceruloplasmin gene variants are associated with hyperferritinemia and increased liver iron in patients with NAFLD[J]. **J Hepatol**, 2021, 75(3): 506-513.
- [40] LIU C, CHEN Y, ZHANG Z, et al. Iron status and NAFLD among European populations: a bidirectional two-sample mendelian randomization study[J]. **Nutrients**, 2022, 14(24): 5237.
- [41] SAYUTI N H, MUHAMMAD NAWAWI K N, GOON J A, et al. Preventative and therapeutic effects of astaxanthin on NAFLD[J]. **Antioxidants (Basel)**, 2023, 12(8): 1552.
- [42] MIYATA T, NAGY L E. Programmed cell death in alcohol-associated liver disease[J]. **Clin Mol Hepatol**, 2020, 26(4): 618-625.
- [43] LIU C Y, WANG M, YU H M, et al. Ferroptosis is involved in alcohol-induced cell death *in vivo* and *in vitro*[J]. **Biosci Biotechnol Biochem**, 2020, 84(8): 1621-1628.
- [44] SHI J F, LIU Y, WANG Y, et al. Targeting ferroptosis, a novel programmed cell death, for the potential of alcohol-related liver disease therapy[J]. **Front Pharmacol**, 2023, 14: 1194343.
- [45] WU J, WANG Y, JIANG R, et al. Ferroptosis in liver disease: new insights into disease mechanisms[J]. **Cell Death Discov**, 2021, 7(1): 276.
- [46] ZHOU Z, YE T J, BONAVIDA G, et al. Adipose-specific lipin-1 overexpression renders hepatic ferroptosis and exacerbates alcoholic steatohepatitis in mice[J]. **Hepatal Commun**, 2019, 3(5): 656-669.
- [47] ZHANG Y, ZHAO S, FU Y, et al. Computational repositioning of dimethyl fumarate for treating alcoholic liver disease[J]. **Cell Death Dis**, 2020, 11(8): 641.
- [48] QI D, CHEN P, BAO H, et al. Dimethyl fumarate protects against hepatic ischemia-reperfusion injury by alleviating ferroptosis via the NRF2/SLC7A11/HO-1 axis[J]. **Cell Cycle**, 2023, 22(7): 818-828.
- [49] DUDAREVA S, FABER M, ZIMMERMANN R, et al. Epidemiology of viral hepatitis A to E in Germany[J]. **Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz**, 2022, 65(2): 149-158.
- [50] COOKE G S, FLOWER B, CUNNINGHAM E, et al. Progress towards elimination of viral hepatitis: a lancet gastroenterology & hepatology commission update[J].

- Lancet Gastroenterol Hepatol**, 2024, 9(4): 346-365.
- [51] WANG R, ZHAO S, DU J, et al. A correlation analysis of the serum hepcidin concentrations and viral loads in HCV-infected patients[J]. **Am J Transl Res**, 2021, 13(6): 6297-6304.
- [52] BIAN Z, HANN H W, YE Z, et al. Ferritin level prospectively predicts hepatocarcinogenesis in patients with chronic hepatitis B virus infection[J]. **Oncol Lett**, 2018, 16(3): 3499-3508.
- [53] ARMITAGE A E, STACEY A R, GIANNOULATOU E, et al. Distinct patterns of hepcidin and iron regulation during HIV-1, HBV, and HCV infections[J]. **Proc Natl Acad Sci U S A**, 2014, 111(33): 12187-12192.
- [54] MA S, LIU A, HU X, et al. Eltrombopag inhibits Type I interferon-mediated antiviral signaling by decreasing cellular iron[J]. **Biochem Pharmacol**, 2021, 186: 114436.
- [55] EZZIKOURI S, NISHIMURA T, KOHARA M, et al. Inhibitory effects of Pycnogenol® on hepatitis C virus replication[J]. **Antiviral Res**, 2015, 113: 93-102.
- [56] CUI X X, YANG X, WANG H J, et al. Luteolin-7-O-Glucoside present in lettuce extracts inhibits hepatitis B surface antigen production and viral replication by human hepatoma cells *in vitro*[J]. **Front Microbiol**, 2017, 8: 2425.
- [57] KOMORI A. Recent updates on the management of autoimmune hepatitis[J]. **Clin Mol Hepatol**, 2021, 27(1): 58-69.
- [58] QIU D, WANG Q, WANG H, et al. Validation of the simplified criteria for diagnosis of autoimmune hepatitis in Chinese patients[J]. **J Hepatol**, 2011, 54(2): 340-347.
- [59] ZHU L, CHEN D, ZHU Y, et al. GPX4-regulated ferroptosis mediates S100-induced experimental autoimmune hepatitis associated with the Nrf2/HO-1 signaling pathway [J]. **Oxid Med Cell Longev**, 2021, 2021: 6551069.
- [60] QU X F, LIANG T Y, WU D G, et al. Acyl-CoA synthetase long chain family member 4 plays detrimental role in early brain injury after subarachnoid hemorrhage in rats by inducing ferroptosis[J]. **CNS Neurosci Ther**, 2021, 27(4): 449-463.
- [61] JIANG H, FANG Y, WANG Y, et al. FGF4 improves hepatocytes ferroptosis in autoimmune hepatitis mice via activation of C1SD3[J]. **Int Immunopharmacol**, 2023, 116: 109762.
- [62] LEE Y A, WALLACE M C, FRIEDMAN S L. Pathobiology of liver fibrosis: a translational success story [J]. **Gut**, 2015, 64(5): 830-841.
- [63] CHO S S, YANG J H, LEE J H, et al. Ferroptosis contribute to hepatic stellate cell activation and liver fibrogenesis[J]. **Free Radic Biol Med**, 2022, 193(Pt 2): 620-637.
- [64] KIM H Y, YOO Y H. Recombinant FGF21 Attenuates polychlorinated biphenyl-induced NAFLD/NASH by modulating hepatic lipocalin-2 expression[J]. **Int J Mol Sci**, 2022, 23(16): 8899.
- [65] TSUCHIDA T, FRIEDMAN S L. Mechanisms of hepatic stellate cell activation[J]. **Nat Rev Gastroenterol Hepatol**, 2017, 14(7): 397-411.
- [66] ZHANG Z, YAO Z, WANG L, et al. Activation of ferritinophagy is required for the RNA-binding protein ELAVL1/HuR to regulate ferroptosis in hepatic stellate cells[J]. **Autophagy**, 2018, 14(12): 2083-2103.
- [67] ZHANG Z, GUO M, LI Y, et al. RNA-binding protein ZFP36/TTP protects against ferroptosis by regulating autophagy signaling pathway in hepatic stellate cells[J]. **Autophagy**, 2020, 16(8): 1482-1505.
- [68] SUI M, JIANG X, CHEN J, et al. Magnesium isoglycyrrhizinate ameliorates liver fibrosis and hepatic stellate cell activation by regulating ferroptosis signaling pathway [J]. **Biomed Pharmacother**, 2018, 106: 125-133.
- [69] WANG L, ZHANG Z, LI M, et al. P53-dependent induction of ferroptosis is required for artemether to alleviate carbon tetrachloride-induced liver fibrosis and hepatic stellate cell activation[J]. **IUBMB Life**, 2019, 71(1): 45-56.
- [70] KONG Z, LIU R, CHENG Y. Artesunate alleviates liver fibrosis by regulating ferroptosis signaling pathway[J]. **Biomed Pharmacother**, 2019, 109: 2043-2053.
- [71] LI L, WANG K, JIA R, et al. Ferroportin-dependent ferroptosis induced by ellagic acid retards liver fibrosis by impairing the SNARE complexes formation[J]. **Redox Biol**, 2022, 56: 102435.
- [72] WANG Y, DENG B. Hepatocellular carcinoma: molecular mechanism, targeted therapy, and biomarkers[J]. **Cancer Metastasis Rev**, 2023, 42(3): 629-652.
- [73] ZHU X, SHA X, ZANG Y, et al. Current progress of ferroptosis study in hepatocellular carcinoma[J]. **Int J Biol Sci**, 2024, 20(9): 3621-3637.
- [74] TAN D, TANG A, LIM W H, et al. Survival trends in sorafenib for advanced hepatocellular carcinoma: a reconstructed individual patient data meta-analysis of randomized trials[J]. **Liver Cancer**, 2023, 12(5): 445-456.
- [75] LOUANDRE C, MARCQ I, BOUHLAL H, et al. The retinoblastoma (Rb) protein regulates ferroptosis induced by sorafenib in human hepatocellular carcinoma cells [J]. **Cancer Lett**, 2015, 356(2 Pt B): 971-977.
- [76] YUAN H, LI X, ZHANG X, et al. C1SD1 inhibits ferroptosis by protection against mitochondrial lipid peroxidation[J]. **Biochem Biophys Res Commun**, 2016, 478(2): 838-844.
- [77] SUN X, OU Z, CHEN R, et al. Activation of the p62-Keap1-NRF2 pathway protects against ferroptosis in hepatocellular carcinoma cells[J]. **Hepatology**, 2016, 63(1): 173-184.
- [78] BAI T, LEI P, ZHOU H, et al. Sigma-1 receptor protects against ferroptosis in hepatocellular carcinoma cells [J]. **J Cell Mol Med**, 2019, 23(11): 7349-7359.

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