

· 综述 ·

DOI: 10.12449/JCH260833

线粒体功能障碍与细胞间通讯在代谢相关脂肪性肝炎中的作用机制

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摘要: 代谢相关脂肪性肝病 (MAFLD) 在脂质毒性、炎症浸润等因素作用下, 肝细胞线粒体稳态失衡并出现功能障碍, 进而进展为代谢相关脂肪性肝炎 (MASH)。近年研究证实, 线粒体损伤与慢性炎症密切相关, 而细胞外囊泡是连接二者的核心媒介。本文系统综述了 MAFLD/MASH 中肝细胞线粒体损伤的分子机制, 重点阐明肝细胞来源细胞外囊泡对肝内炎症的调控作用, 并探讨线粒体靶向治疗及细胞间通讯干预在 MAFLD/MASH 中的潜在应用前景, 旨在为开发此类疾病的新型治疗策略提供理论依据。

关键词: 代谢相关脂肪性肝炎; 线粒体功能障碍; 细胞外囊泡; 细胞间通讯

基金项目: 浙江省自然科学基金 (ZCLQN25H0306); 浙江省医药卫生科技计划项目 (2025KY356); 嘉兴市科技计划项目 (2024AY40023, 2024AY30020)

Mechanism of action of mitochondrial dysfunction and intercellular communication in metabolic dysfunction-associated steatohepatitis

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Abstract: Metabolic dysfunction-associated fatty liver disease (MAFLD) progresses to metabolic dysfunction-associated steatohepatitis (MASH) due to mitochondrial homeostasis imbalance and dysfunction in hepatocytes caused by various factors such as lipotoxicity and inflammatory infiltration. Recent studies have confirmed that mitochondrial injury is closely associated with chronic inflammation, with extracellular vesicle (EV) acting as a key mediator linking the two processes. This article systematically reviews the molecular mechanisms of hepatocyte mitochondrial dysfunction in MAFLD/MASH, highlights the regulatory role of hepatocyte-derived EV in intrahepatic inflammation, and discusses the potential application prospects of mitochondria-targeted therapies and intercellular communication interventions in MAFLD/MASH, in order to provide a theoretical basis for developing novel therapeutic strategies for these diseases.

Key words: Metabolic Dysfunction-Associated Steatohepatitis; Mitochondrial Dysfunction; Extracellular Vesicles; Cell Communication

Research funding: Natural Science Foundation of Zhejiang Province (ZCLQN25H0306); Medical and Health Science and

Technology Project of Zhejiang Province (2025KY356); The Science and Technology Program of Jiaxing (2024AY40023, 2024AY30020)

近年来,代谢相关脂肪性肝病(metabolic dysfunction-associated fatty liver disease, MAFLD)的患病率持续上升,目前约38%的成人、7%~14%的儿童/青少年受累,预计至2040年,成人患病率将超过55%^[1]。MAFLD是脂肪性肝病的主要亚型,在脂肪性肝病中占比达89%^[2],其严重进展形式为代谢相关脂肪性肝炎(metabolic dysfunction-associated steatohepatitis, MASH),核心特征是代谢紊乱与炎症并存。肝脏线粒体通过调控脂质代谢与氧化应激维持肝功能^[3],但在MASH状态下,其形态、动力学等多维度出现异常,且功能障碍与炎症浸润形成恶性循环——线粒体可通过炎症因子、细胞外囊泡(extracellular vesicle, EV)介导细胞间通讯,活化炎症细胞,进而推动疾病进展,导致MASH患者的肝病进展,死亡风险显著升高。本文围绕肝脏线粒体功能障碍,聚焦慢性炎症与细胞间通讯,阐述EV介导的炎症细胞活化机制。

1 肝细胞线粒体功能障碍

肝脏是机体的代谢中心,负责能量稳态维持、生物分子合成及代谢物清除。上述过程依赖于肝细胞线粒体的功能稳态,而线粒体需根据代谢信号与应激刺激进行精准调控,以满足细胞的动态需求。任一环节的调控紊乱均会破坏线粒体功能网络,诱发线粒体功能障碍,进而推动疾病病理进程。MASH患者的肝组织中,已明确存在线粒体形态、融合-分裂、生物发生、自噬等多维度调控异常。

1.1 线粒体形态与结构 线粒体结构稳定是其功能正常的基础,MASH患者肝细胞内线粒体常呈多种异常形态,包括肿胀变圆、膜结构多层化、嵴断裂消失,甚至形成巨型线粒体。这类巨型线粒体虽定位分布随机、规律不明,但常与马洛里小体、脂肪沉积共现^[4],且推测其与胞内脂肪滴、透明质体可能存在结构关联。

1.2 线粒体动力学 分裂与融合是线粒体动力学的核心过程,线粒体分裂由动力相关蛋白1寡聚化形成的收缩环驱动,线粒体分裂蛋白1、线粒体裂变因子等可辅助其精准定位;线粒体融合则由线粒体融合蛋白1/2、视神经萎缩蛋白1分别调控外膜与内膜的融合。二者协同调控线粒体的数量、大小与胞内分布,维持线粒体网络的连通性。在细胞增殖分裂、能量需求降低、线粒体损伤

及氧化应激状态下,线粒体以分裂为主,可实现子代分配、损伤片段分离与代谢适配;而在细胞静息、高能量需求、线粒体轻度损伤及胞内钙稳态波动时,则以融合为主,可提升氧化磷酸化效率、修复线粒体损伤并维持膜电位稳定。线粒体的分裂与融合并非相互独立的过程,腺苷酸活化蛋白激酶、蛋白激酶C等可通过介导蛋白修饰对二者实现交叉调控,从而快速启动分裂与融合反应。线粒体膜电位是调控线粒体分裂与融合平衡的核心开关,健康线粒体的高膜电位可促进线粒体融合,损伤线粒体的低膜电位则会抑制融合并促进分裂,从而完成对损伤线粒体修复与清除的定向调控。此外,通过调控线粒体动力学蛋白的转录表达水平,可适配细胞稳态状态,实现代谢需求的长期动态平衡。

在MASH疾病进程中,代谢紊乱与线粒体动力学受损密切相关。肝特异性缺失线粒体裂变因子的小鼠,即使在普通饲料喂养条件下,也可出现线粒体形态异常;改为高脂饮食后,可迅速发展为典型MASH表型^[5];抑制线粒体融合亦能阻止巨型线粒体堆积,并逆转已确立的炎症与纤维化^[6]。尽管线粒体动力学在MASH进展中的作用,以及线粒体分裂与融合的主次影响仍有待进一步探索,但可以明确的是,线粒体体积过大或过小均不利于功能稳态维持,分裂与融合的动态平衡对保障线粒体整体功能稳定至关重要。

1.3 线粒体生物发生和自噬 线粒体生物发生是指线粒体的“新生与扩增”过程,由过氧化物酶体增殖物激活受体 γ 共激活因子1 α (peroxisome proliferator-activated receptor gamma coactivator 1-alpha, PGC-1 α)主控:PGC-1 α 先激活核呼吸因子1/2,同步上调核基因与线粒体基因的表达,再经线粒体转录因子A启动线粒体DNA转录^[7]。在MAFLD患者肝细胞内,PGC-1 α 表达下调,线粒体更新受阻^[8];激活过表达沉默信息调节因子1可迅速唤醒PGC-1 α ,恢复线粒体生物发生,活性氧与脂滴积聚亦得到一定程度缓解^[9-10]。上述证据共同表明,MAFLD的肝脏并非单纯“脂肪过多”,而是线粒体“产能线”更新受阻。

线粒体自噬与线粒体生物发生呈现数量拮抗、功能协同,本质上共同维系线粒体池的更新:自噬清除分裂后受损的细胞器以控制数量,生物发生则补充新生线粒体。高活性线粒体网络不仅依赖新生速率,更取决于损

伤线粒体的清除效率。在MASH肝细胞中,线粒体自噬受到抑制,更新平衡被打破^[11-12]。研究发现,MYC相互作用锌指蛋白1的缺失会进一步阻碍线粒体自噬,导致受损线粒体积累,并进一步下调MYC相互作用锌指蛋白1表达,形成正反馈循环,加剧自噬抑制与炎症反应^[13]。

2 肝细胞来源EV在MASH慢性炎症网络中的调控作用

细胞间通讯是维系生理功能、应对病理变化的关键环节,EV为其重要载体,可分为外泌体、微囊泡与凋亡小体^[14]。在肝脏疾病、风湿性疾病、急性炎症、癌症等多种炎症相关疾病中,EV水平升高的现象已被广泛证实^[15-18]。这类EV携带供体细胞的生物活性分子,调控受体细胞的病理生理过程,或通过释放内容物改变细胞微环境^[19]。在MASH的病理进程中,肝细胞线粒体功能障碍可通过EV作为载体放大损伤效应,靶向作用于肝非实质细胞,进一步促进炎症活化并加剧纤维化进程,是连接线粒体损伤与肝内慢性炎症的核心纽带。

2.1 肝细胞来源EV装载受损线粒体 当线粒体损伤程度显著加重时,线粒体自噬难以有效清除受损线粒体。甲酰胺、线粒体DNA等损伤相关分子可由肝细胞释放至细胞外,引发广泛病理效应,该现象被称为“线粒体损伤相关分子模式”。近期研究表明,线粒体及其损伤分子可通过EV传递,而EV的参与进一步扩大了损伤信号的扩散范围^[15-16]。

在MASH病理进程中,线粒体损伤机制错综复杂,线粒体损伤与自噬受阻协同作用,导致细胞内损伤线粒体负荷升高;与此同时,高脂饮食模型中,棕榈酸及其活性代谢物溶血磷脂酰胆碱刺激肝细胞可显著上调EV分泌^[20];缺氧亦同步增强体内外肝细胞来源EV的释放^[21]。疾病状态下的肝细胞成为细胞间通讯的主体细胞之一,线粒体损伤与EV分泌亢进的双重病变,可激活囊泡外排途径,将“难以清除”的线粒体片段装入EV^[22],从而将局部代谢危机转化为可扩散的炎症信号,既是损伤级联的促进因素,也可靶向肝内巨噬细胞、中性粒细胞与肝星状细胞(hepatic stellate cell, HSC),重塑其趋化、极化及活化程序。

2.2 肝细胞-巨噬细胞来源EV通讯 肝脏巨噬细胞群体由组织驻留的库普弗细胞及骨髓来源的单核细胞衍生巨噬细胞共同构成,二者均密集分布于肝窦内,是感应损伤信号并启动炎症级联的核心免疫细胞。当肝细胞受到脂质毒性、乙醇或代谢应激时,其释放的EV可精

准靶向上述巨噬细胞,通过一次性递送趋化因子、损伤相关分子模式及微小RNA等活性分子,显著增强巨噬细胞的定向迁移、表型极化及促炎因子分泌能力,从而将最初的肝细胞损伤转化为持续且放大的肝脏炎症。

肝细胞内肌醇需求酶1 α -X盒结合蛋白1信号通路可通过转录上调丝氨酸棕榈酰转移酶,促进神经酰胺合成,进而驱动EV释放并介导单核-巨噬细胞招募^[23]。EV携带的微小RNA亦参与巨噬细胞重编程:脂毒性肝细胞经EV将微小RNA-9-5p传递至巨噬细胞,通过抑制转谷氨酰胺酶2促进M1型极化,加剧肝脏炎症^[24];富含微小RNA-192-5p的外泌体通过靶向雷帕霉素不敏感伴侣蛋白,抑制蛋白激酶B/叉头框蛋白O1信号通路,阻断巨噬细胞M2型极化维持并增强M1型促炎表型,从而加速疾病进程^[25]。线粒体同样参与EV介导的病理过程:受损肝细胞分泌的EV中,线粒体DNA及线粒体蛋白含量显著升高,可通过Toll样受体9依赖途径刺激巨噬细胞分泌白细胞介素1 β 与白细胞介素17A,后者表达上调幅度可达百倍,进一步放大线粒体损伤相关分子模式信号^[26]。尤为关键的是,EV可介导脂质积聚与炎症放大的正反馈环路:EV递送的视黄醇结合蛋白4激活巨噬细胞还原型烟酰胺腺嘌呤二核苷酸磷酸氧化酶2-活性氧-核因子 κ B通路,诱导M1型极化并分泌肿瘤坏死因子 α ;肿瘤坏死因子 α 通过信号转导与转录激活因子3反向上调肝细胞视黄醇结合蛋白4表达,形成“脂质-炎症”闭环,使肝脂肪沉积与炎症反应互为因果、持续恶化^[27]。

2.3 肝细胞-中性粒细胞来源EV通讯 MAFLD进展至MASH阶段时,受损肝细胞释放趋化因子,募集中性粒细胞并激活早期炎症^[28-29]。活化后的中性粒细胞通过脱颗粒、中性粒细胞胞外陷阱(neutrophil extracellular trap, NET)形成、呼吸爆发、蛋白酶释放等途径发挥病理作用^[30]。过度生成的NET可介导肝脏多维度病理损伤:其一,NET上调白细胞介素1 β 与白细胞介素17A的表达,激活巨噬细胞,进而诱导肝细胞衰老及脂质蓄积^[31];其二,NET诱发机体高凝状态并损伤肝血管内皮,加剧肝内纤维蛋白沉积^[32]。此外,NET能够诱导HSC发生代谢重编程,协同促进肝纤维化进展^[33]。同时,NET可塑造肝脏促肿瘤微环境,诱导调节性T细胞分化,为肝细胞癌的发生发展提供有利条件^[34]。

NET的生成离不开肝细胞与中性粒细胞经EV完成的跨细胞信号交互。中性粒细胞经低密度脂蛋白受体-载脂蛋白E通路将微小RNA-223装入EV,输回肝细胞,产生抗炎-抗纤维化效应,减缓MASH进程^[35]。然而在肝

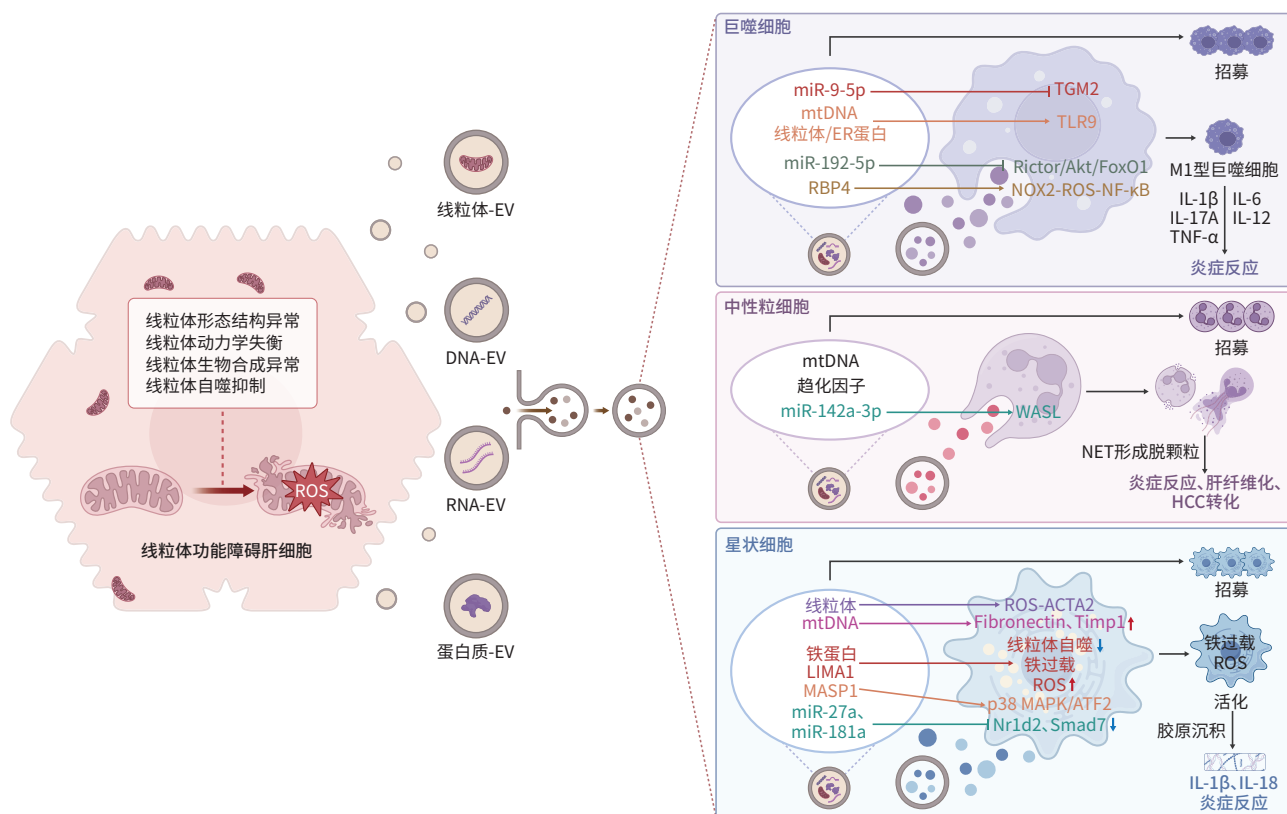
病状态下, EV 成为“反向推手”, 即肝细胞来源 EV 直接诱导中性粒细胞迁移^[36]; 乙醇激活凋亡信号调节激酶 1/p38 α 丝裂原活化蛋白激酶轴, 促使肝细胞释放富含线粒体 DNA 的 EV, 招募中性粒细胞并递送代谢危机信号, 瞬间触发 NET 形成, 将能量应激升级为炎症风暴^[37]。EV 携带微 RNA-142a-3p 抑制神经型韦斯科特-奥尔德里奇综合征蛋白表达, 亦可直接刺激 NET 形成^[38]。

2.4 肝细胞-HSC 来源 EV 通讯 肝内炎症迁延, HSC 持续分泌胶原, 纤维隔成型; 成纤维细胞激活蛋白在沉积过程的同时激活巨噬细胞, 形成纤维化-炎症正反馈^[39]。

棕榈酸处理的肝细胞释放 EV 对活化 HSC 具有显著趋向性^[40]; 脂肪肝来源 EV 自带脂肪酸应激分子, 即使无炎症, 亦可驱动 HSC 趋化-增殖-肌成纤维母细胞转化, 完成代谢-纤维化转化^[41]。p53-帕金蛋白轴将完整线粒体封入 EV, 通过横向输能并触发活性氧-肌动蛋白 $\alpha 2$ 轴, 显著增强 HSC 迁移与胶原生成^[42]; 在四氯化碳或对

乙酰氨基酚诱导的急性肝损伤模型中, 线粒体 DNA 经 EV 毒化邻近 HSC^[43]; 铁蛋白-富铁 EV 可抑制线粒体自噬, 导致活性氧大量堆积, 推进纤维化表型进展^[44]。LIM 结构域与肌动蛋白结合蛋白 1 同样阻断 HSC 系 LX2 的线粒体自噬, 并促进其激活^[45]; β 抑制蛋白 1 促进 EV 装载富含甘露聚糖结合凝集素相关丝氨酸蛋白酶 1, 继而激活 p38 丝裂原活化蛋白激酶/活化转录因子 2 通路, 诱导 HSC 活化^[46]。相反, 静息状态的肝细胞来源 EV 则可控制纤维化, 其内含有的微 RNA-423-5p 可靶向抑制 α -平滑肌肌动蛋白以及 I 型胶原蛋白 α 链, 维持 HSC 处于非激活表型; 乙醇或月桂酸应激可显著下调该微 RNA 的表达, 导致“刹车”失灵^[47]。此外, 内含微 RNA-27a、微 RNA-181a 等的 EV 亦可靶向抑制 HSC 静息状态的基因, 从而顺势启动激活程序^[26]。

图 1 归纳了肝细胞来源 EV 与巨噬细胞、中性粒细胞及 HSC 的互作模式, 以阐明其作用机制。



注: EV, 细胞外囊泡; mtDNA, 线粒体 DNA; miR, 微 RNA; ER, 内质网; RBP4, 视黄醇结合蛋白 4; TGM2, 转谷氨酰胺酶 2; TLR9, Toll 样受体 9; Rictor, 雷帕霉素不敏感伴侣蛋白; Akt, 蛋白激酶 B; FoxO1, 叉头框蛋白 O1; NOX2, 还原型烟酰胺腺嘌呤二核苷酸氧化酶 2; ROS, 活性氧; NF- κ B, 核因子 κ B; IL, 白细胞介素; TNF- α , 肿瘤坏死因子 α ; M1, 巨噬细胞 M1 型(促炎型); WASL, 韦斯科特-奥尔德里奇综合征蛋白样肌动蛋白成核促进因子; NET, 中性粒细胞胞外陷阱; HCC, 肝细胞癌; LIM1, LIM 结构域与肌动蛋白结合蛋白 1; MASP1, 甘露聚糖结合凝集素相关丝氨酸蛋白酶 1; ACTA2, α -平滑肌肌动蛋白 2; Fibronectin, 纤维连接蛋白; Timp1, 金属蛋白酶组织抑制剂 1; p38 MAPK, p38 丝裂原活化蛋白激酶; ATF2, 活化转录因子 2; Nr1d2, 核受体亚家族 1D 组成员 2; Smad7, 母系抗十五表态蛋白同源物 7; MASH, 代谢相关脂肪性肝炎。

图 1 肝细胞来源 EV 在 MASH 慢性炎症网络中的调控作用

Figure 1 Regulation of hepatocyte-derived extracellular vesicle in the chronic inflammatory network of MASH

3 治疗靶点

针对线粒体功能障碍的治疗策略,对于打破“能量危机-炎症-纤维化”这一连锁反应、改善疾病进展以及优化患者预后具有至关重要的作用。

3.1 生活方式干预 生活方式干预包括饮食调整及规律运动,是MASH管理的重要环节。地中海饮食富含多不饱和脂肪酸,经研究证实可增强线粒体生物发生与功能,改善代谢健康^[48]。规律运动亦能通过多途径改善线粒体功能,如提升超氧化物歧化酶、过氧化氢酶等抗氧化酶活性,清除线粒体活性氧以减轻氧化应激;同时改善线粒体 β -氧化功能、促进脂肪酸代谢,增强电子传递链功能以提升能量生成效率^[49]。

3.2 靶向药物治疗 通过调节线粒体的病理生理过程以纠正其功能障碍,有望从根源上解决肝内代谢紊乱,以线粒体为靶点的治疗策略逐渐成为药物研发的热点领域。

瑞美替罗(Resmetirom)是首个获得美国食品药品监督管理局批准用于治疗伴有中重度肝纤维化的MASH的口服药物。该药通过减少脂肪生成、促进脂肪酸氧化及线粒体生物发生,改善肝纤维化^[50]。除瑞美替罗外,目前尚有多种线粒体靶向药物正处于积极研究阶段,包括白藜芦醇、烟酰胺腺嘌呤二核苷酸前体激活沉默信息调节因子1-PGC-1 α 轴,提升线粒体呼吸功能并降低脂质水平^[51]。

3.3 以EV介导线粒体转移为靶点的治疗策略 EV既能放大炎症、恶化疾病,亦可作为治疗靶点。近期研究证实,超纯化间充质干细胞可通过隧道纳米管、Cx43间隙连接通道及EV 3条路径,将完整线粒体转移至受体细胞,修复线粒体DNA并恢复能量代谢^[52]。间充质干细胞来源EV携带的线粒体成分可恢复受损受体细胞内线粒体的稳定性,逆转线粒体DNA缺失和氧化磷酸化缺陷,从而减轻线粒体损伤^[53]。在多种肝病模型中,间充质干细胞来源EV通过靶向抑制动力相关蛋白1,减轻线粒体过度分裂,显著改善肝细胞脂肪变性并延缓MAFLD进展^[54];搭载环指蛋白31的间充质干细胞来源EV在体内干预更加高效,仅治疗4周,肝脂滴沉积明显减少,线粒体膜电位恢复,肝酶水平下降,肝细胞凋亡显著减少^[12]。抗炎型骨髓来源巨噬细胞分泌的EV通过富集胆固醇结合蛋白相关蛋白8,缓解内质网应激,抑制脂质毒性及炎症反应,从而显著改善MASH^[55]。上述成果共同提示,以EV为载体的干预策略在改善MASH方面具有广阔的

应用前景。此外,针对免疫细胞稳态的维持也有相关研究支持。脂肪间充质干细胞来源EV可向巨噬细胞递送线粒体成分,提升其氧化磷酸化效率与膜完整性,重建巨噬细胞的代谢及免疫稳态,显著缓解炎症^[56];间充质干细胞来源EV将功能性线粒体或锰超氧化物歧化酶靶向送入中性粒细胞,诱导线粒体融合、恢复膜电位,抑制NET释放和内皮细胞铁死亡,在减轻氧化应激的同时加速组织愈合^[57]。

4 小结与展望

MAFLD/MASH的线粒体功能障碍表现为多种机制参与下的稳态失衡。本文系统阐述了存在线粒体功能障碍的肝细胞可通过EV将“代谢危机”转化为系统性炎症信号,向库普弗细胞、中性粒细胞及HSC递送危险信号,触发多条信号通路,促进白细胞介素1 β 、肿瘤坏死因子 α 、NET及胶原生成,形成“能量损伤-囊泡扩散-免疫细胞激活-纤维化”级联反应。反之,间充质干细胞来源EV可向肝细胞及炎症细胞递送完整线粒体或“有益成分”,修复线粒体DNA、稳定线粒体膜电位、恢复氧化磷酸化并稳定下游细胞,从而阻断恶性循环。临床前研究证实,该策略可显著减轻脂肪变性、炎症浸润与纤维化,提示EV介导的细胞通讯网络既是疾病进展的核心驱动因素,也为干预治疗开辟了新路径。

尽管EV介导的细胞通讯网络在肝病研究中已取得进展,但仍存在诸多不足。后续研究可聚焦于以下4个方面:(1)深化中性粒细胞与肝细胞之间的通讯机制研究;(2)突破单向研究视角,以双向或网络思维解析“肝细胞-免疫细胞-肝细胞”闭环反馈,如脂毒性EV激活巨噬细胞/库普弗细胞后,后者通过炎症信号影响肝细胞胰岛素通路形成的恶性循环^[20];(3)研发靶向线粒体功能障碍的小分子或生物制剂,从源头阻断损伤;(4)靶向细胞间通讯关键节点,设计可临床转化的干预技术,以切断恶性循环。综上所述,未来需聚焦代谢与炎症的通讯网络,为MASH治疗提供理论支撑。

利益冲突声明: 本文不存在任何利益冲突。

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收稿日期: 2025-12-10; 录用日期: 2026-02-02

本文编辑: 葛俊

引证本文: 罗婉艺, 张津铭, 于牧鑫, 等. 线粒体功能障碍与细胞间通讯在代谢相关脂肪性肝炎中的作用机制[J]. 临床肝胆病杂志, 2026, 42(8): 1967-1973.

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