

· 综述 ·

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线粒体DNA释放触发的先天免疫机制在代谢相关脂肪性肝病中的作用及靶向干预策略

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摘要: 代谢相关脂肪性肝病(MAFLD)是全球发病率最高的慢性肝病,其发病机制复杂。线粒体在该疾病进程中发挥关键作用,研究证实线粒体功能障碍可加剧代谢紊乱、诱发先天免疫失衡,而线粒体DNA(mtDNA)是介导这两大病理效应的核心分子。mtDNA异常释放后,可被细胞内模式识别受体识别,进而触发先天免疫反应并引发组织损伤,形成“mtDNA释放-免疫激活-组织损伤”的病理通路。目前,该通路在MAFLD疾病不同阶段的作用机制以及靶向该通路的干预策略,尚缺乏系统性的综述总结。本文系统综述该通路的核心分子机制、在MAFLD发生发展中的病理作用及当前靶向该机制的干预策略,旨在为MAFLD的病理机制解析与新型治疗策略的开发提供理论依据。

关键词: 代谢相关脂肪性肝病; DNA; 线粒体; 免疫; 先天; 信号传导

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Role of innate immune mechanisms triggered by mitochondrial DNA release in metabolic dysfunction-associated fatty liver disease and targeted intervention strategies

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Abstract: Metabolic dysfunction-associated fatty liver disease (MAFLD) is the most prevalent chronic liver disease worldwide, with a complex pathogenesis. Mitochondria play a pivotal role in this disease process, and studies have confirmed that mitochondrial dysfunction can exacerbate metabolic disorders and induce innate immune imbalance, while mitochondrial DNA (mtDNA) is the core molecule mediating these two pathological effects. After the abnormal release of mtDNA, it can be recognized by intracellular pattern recognition receptors, which in turn triggers innate immune responses and causes tissue damage, forming a pathological pathway of “mtDNA release-immune activation-tissue damage”. Currently, there is a lack of systematic reviews summarizing the mechanism of action of this pathway in different stages of MAFLD and the intervention strategies targeting this pathway. This article systematically reviews the core molecular mechanism of this pathway, its pathological role in the development and progression of MAFLD, and the current intervention strategies targeting this mechanism, in order to provide a theoretical basis for analyzing the pathogenesis of MAFLD and developing novel therapeutic strategies.

Key words: Metabolic Dysfunction-Associated Fatty Liver Disease; DNA, Mitochondrial; Immunity, Innate; Signal Transduction

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随着全球肥胖、2型糖尿病及代谢综合征患者数量的增加,代谢相关脂肪性肝病(metabolic dysfunction-associated fatty liver disease, MAFLD)的患病率持续上升,已成为全球范围内发病率最高的慢性肝病^[1]。目前,其发病机制尚未完全阐明。已有研究表明,过度的脂质堆积、胰岛素抵抗等代谢应激会诱导肝细胞损伤,这种损伤信号可激活先天免疫反应,促使免疫细胞或肝细胞释放大促炎因子,进一步加重肝细胞损伤与代谢紊乱,形成恶性循环^[2]。线粒体是肝细胞能量代谢的核心与活性氧(reactive oxygen species, ROS)产生的主要场所,其功能障碍是代谢应激与免疫失衡的关键桥梁^[3]。在MAFLD发生发展过程中,线粒体会率先出现结构和功能的损伤,导致线粒体DNA(mitochondrial DNA, mtDNA)异常释放,释放的mtDNA作为内源性损伤相关分子模式触发先天免疫反应^[4]。目前,已证实该机制在MAFLD向代谢相关脂肪性肝炎(metabolic dysfunction-associated steatohepatitis, MASH)转化、肝纤维化进展中发挥关键作用,针对该机制的干预策略也逐步进入基础研究与早期临床探索阶段。本文将系统阐述mtDNA释放触发先天免疫的核心机制、该通路在MAFLD中的病理作用及干预策略,为MAFLD新型治疗药物的开发提供理论依据与方向。

1 mtDNA释放触发先天免疫的核心分子机制

1.1 mtDNA的免疫源性特征与释放机制 mtDNA是存在于线粒体基质中的环状双链DNA,与核DNA相比具有显著的结构特殊性,使其具备强大的免疫激活潜力^[5]。从结构特征来看,mtDNA不与核DNA特有的组蛋白相结合,无典型的染色质结构保护(仅与线粒体转录因子A等类组蛋白结合以维持结构),且其序列与细菌DNA高度同源,携带的CpG基序呈现低甲基化状态,这使机体先天免疫系统更容易将其识别为“外来入侵物”^[6]。

正常生理状态下,mtDNA位于线粒体基质内,与细胞质及细胞外环境中的免疫识别受体保持物理隔离;而当线粒体结构受损时,mtDNA会释放至细胞质或细胞外,打破原有隔离状态,成为启动免疫反应的“危险信

号”^[7]。此外,mtDNA的释放常与ROS的产生相关——二者均由线粒体结构损伤诱发,ROS会进一步修饰mtDNA,增强其免疫刺激性,形成“mtDNA释放-ROS生成-免疫激活增强”的病理效应^[8]。上述特征共同赋予mtDNA独特的免疫源性,使其成为连接线粒体损伤与先天免疫激活的核心分子。

mtDNA的释放源于线粒体稳态失衡,主要由外源性应激与内源性病理因素引起。外源性应激包括氧化应激、感染和毒物暴露;内源性病理因素涉及代谢紊乱、自噬缺陷、遗传突变和细胞衰老^[9-10]。

mtDNA释放主要涉及以下3种机制:(1)通过外膜中的BAK/BAX孔隙开放,引发内膜向开放的外膜孔隙突出并释放内容物;或经内膜的线粒体通透性转换孔开放、与外膜的电压依赖性阴离子通道协同调控的跨膜通路逸出。(2)因线粒体吞噬缺陷(受损的线粒体无法清除)、自噬异常(线粒体降解受阻)或膜运输障碍,导致线粒体膜完整性破坏或溶酶体膜泄漏,促使mtDNA从破损结构中逃逸。(3)通过线粒体来源的细胞外囊泡释放进入循环^[11]。

1.2 细胞质与细胞外mtDNA识别通路及交互调控 释放的mtDNA被称为损伤相关分子模式,因其结构特征(如低甲基化的CpG岛)与细菌DNA相似,可通过细胞质与细胞外两条途径被不同信号通路和模式识别受体识别,引发先天免疫反应。其中,细胞质通路中的环鸟苷酸-腺苷酸合酶(cyclic guanosine monophosphate-adenosine monophosphate synthase, cGAS)-干扰素基因刺激因子(stimulator of interferon gene, STING)通路和核苷酸结合寡聚结构域样受体家族热蛋白结构域相关蛋白3(nucleotide-binding oligomerization domain-like receptor family and pyrin domain-containing protein 3, NLRP3)炎症小体,以及细胞外通路中的Toll样受体9(Toll-like receptor 9, TLR9)通路最为关键^[12](图1)。

细胞质DNA传感器cGAS可特异性识别并结合细胞质中释放的mtDNA而被激活,激活后的cGAS催化三磷酸鸟苷与三磷酸腺苷合成第二信使环鸟苷酸-腺苷酸;环鸟苷酸-腺苷酸结合内质网上的STING并诱导其二聚体发生构象变化形成寡聚体。寡聚化的STING转移至高尔基

体上,招募并激活TANK结合激酶1(促进其自身磷酸化),激活的TANK结合激酶1特异性磷酸化细胞质中的干扰素调节因子3,使其进入细胞核,启动I型干扰素的转录与表达;同时,STING可激活I κ B激酶复合物,促使核因子 κ B(nuclear factor- κ B, NF- κ B)二聚体入核,启动I型干扰素及肿瘤坏死因子 α (tumor necrosis factor- α , TNF- α)、白细胞介素(interleukin, IL)6等促炎细胞因子的大量表达,最终启动广谱免疫反应并引发炎症^[13-14]。

NLRP3炎症小体由传感器蛋白NLRP3、含CARD结构域的凋亡相关斑点样蛋白(apoptosis-associated speck-like protein containing a CARD, ASC)和胱天蛋白酶(Caspase)1前体组成,需依赖“双信号”触发激活,而mtDNA参与这两种双信号的调控。第一信号(启动信号):由病原体相关分子模式或损伤相关分子模式通过模式识别受体识别后,激活干扰素调控因子1入核,结合mtDNA驱动胞苷/尿苷单磷酸激酶2蛋白的表达,进一步生成“新的mtDNA”(即在第一信号激活后才产生的mtDNA),为后续激活奠定物质基础;第二信号(激活信号):新合成mtDNA优先进入细胞质,并被线粒体ROS氧化为氧化mtDNA;氧化mtDNA可直接结合NLRP3炎症小体的NACHT结构域并促其寡聚化,NLRP3炎症小体的PYD结构域又招募ASC,ASC再通过Caspase激活与募集结构域结合Caspase-1前体并使其活化;活化的Caspase-1裂解促IL-1 β 、促IL-18的前体,生成成熟的IL-1 β 和IL-18并释放至细胞外,引发炎症级联反应^[15-16]。

TLR9主要表达于免疫细胞(如肝巨噬细胞、外周巨噬细胞)的内体膜上,其对mtDNA的特异性识别依赖内体酸性环境:细胞外mtDNA先通过细胞吞噬、胞饮等内吞作用

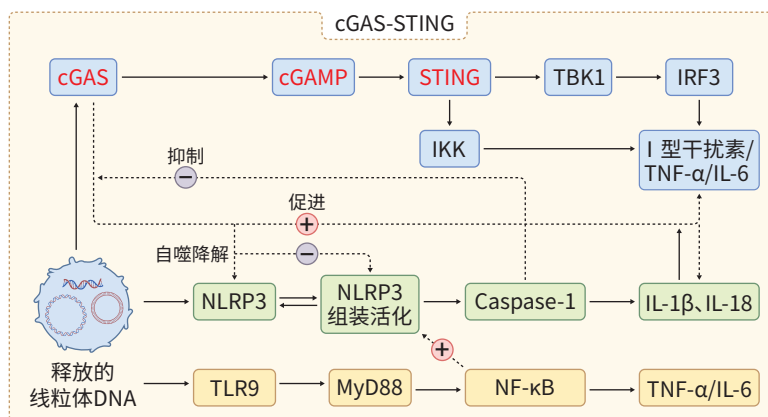
被摄入细胞,形成内体mtDNA;随后内体mtDNA中的低甲基化CpG基序与内体膜上的TLR9特异性结合,激活髓系分化初级反应蛋白质88依赖的信号通路,最终激活NF- κ B,促进TNF- α 、IL-6等炎症因子表达,这些炎症因子共同作用,最终引发并放大肝脏局部或系统性炎症反应^[17-18]。

mtDNA介导的先天免疫通路并非孤立存在,而是通过复杂的交互调控形成网络信号通路,共同调节免疫反应的强度与持续时间^[19]。一方面,通路间存在协同激活效应:例如,cGAS-STING通路激活产生的I型干扰素可上调NLRP3与IL-1 β 的表达,直接增强后续的免疫反应;NLRP3炎症小体释放的IL-1 β 可激活NF- κ B,进一步促进cGAS与STING的转录,形成反馈环路^[20-21]。另一方面,通路间存在拮抗调控作用:例如,STING激活后可通过诱导自噬降解NLRP3,进而间接抑制NLRP3炎症小体的组装与活化,防止炎症过度发展;TLR9通路可通过信号交叉间接促进Caspase-1激活(如通过NF- κ B增强NLRP3炎症小体活性),而活化的Caspase-1会切断cGAS蛋白,导致其催化合成的环鸟苷酸-腺苷酸减少,进一步抑制炎症信号的传导^[22-24]。

在MAFLD的病理状态下,这种协同与拮抗的平衡会被打破,cGAS-STING对NLRP3的激活作用通常强于自噬的抑制作用,导致免疫过度激活,加剧疾病进展^[25-26](图1)。

2 mtDNA-先天免疫通路在MAFLD中的病理作用

2.1 驱动疾病进展:从肝细胞损伤到肝纤维化 单纯性脂肪肝向MASH进展的关键特征是肝细胞损伤与炎症浸润,mtDNA-先天免疫通路在此过程中发挥驱动作



注:cGAS,环鸟苷酸-腺苷酸合酶;cGAMP,环鸟苷酸-腺苷酸;STING,干扰素基因刺激因子;TBK1,TANK结合激酶1;IRF3,干扰素调节因子3;IKK,I κ B激酶;TNF- α ,肿瘤坏死因子 α ;IL-6,白细胞介素6;NLRP3,核苷酸结合寡聚结构域样受体家族热蛋白结构域相关蛋白3;Caspase-1,胱天蛋白酶1;IL-1 β ,白细胞介素1 β ;IL-18,白细胞介素18;TLR9,Toll样受体9;MyD88,髓系分化初级反应蛋白质88;NF- κ B,核因子 κ B。

图1 线粒体DNA触发先天免疫机制的信号通路

Figure 1 Signal pathway of innate immune mechanisms triggered by mitochondrial DNA

用^[27]。MAFLD患者肝脏中过量的脂质堆积会导致线粒体脂质毒性,使线粒体膜电位下降、结构破裂,释放mtDNA至细胞质中^[28];异常释放的mtDNA能激活cGAS-STING通路(调控NF- κ B、干扰素调节因子3等转录因子)与NLRP3炎症小体(活化Caspase-1),产生下游效应。cGAS-STING通路通过NF- κ B激活,促进TNF- α 、IL-6的表达与分泌;NLRP3炎症小体通过活化Caspase-1,介导IL-1 β 的成熟与释放^[14-15]。这些促炎因子共同作用于肝细胞,一方面通过激活凋亡信号通路诱导肝细胞凋亡,另一方面通过增强脂质过氧化反应加重肝细胞脂毒性损伤^[29-30];同时,线粒体损伤及免疫激活会加剧ROS的生成,ROS进一步破坏线粒结构,促使更多mtDNA释放,形成“线粒体损伤-mtDNA释放-免疫激活-肝细胞损伤”的恶性循环^[29]。

由此可见,mtDNA-先天免疫通路可能是驱动这一循环的关键纽带。这一机制的阐明,不仅深化了对MAFLD疾病进展规律的认知,更为后续开发靶向mtDNA释放、cGAS-STING通路或NLRP3炎症小体的MASH治疗策略,提供了重要的理论依据与潜在靶点方向。

肝纤维化是MAFLD进展至肝硬化与肝细胞癌的关键阶段,其核心病理变化是肝星状细胞(hepatic stellate cell, HSC)的活化与胶原沉积,mtDNA-先天免疫通路是驱动HSC活化的重要机制^[31]。mtDNA通过激活cGAS-STING、NLRP3等先天免疫通路,诱导免疫细胞(如巨噬细胞)或肝细胞分泌TNF- α 、IL-6、IL-1 β 等促炎因子;这些因子直接作用于HSC,促使其从静息状态转化为活化的肌成纤维细胞样表型,显著增强I型胶原等细胞外基质的合成能力^[32-33]。肝巨噬细胞可通过吞噬细胞外mtDNA进入内体,再由内体中的TLR9识别mtDNA并被激活,进一步极化为促炎的经典活化巨噬细胞表型:一方面自身释放大量的促炎因子(如TNF- α)与趋化因子(如C-C趋化因子配体2);另一方面招募外周单核细胞分化为巨噬细胞浸润肝脏,形成“免疫细胞浸润→炎症放大”的效应,共同促进HSC的活化^[34-35]。动物实验证实,敲除STING或NLRP3基因的MAFLD小鼠,其肝脏胶原沉积与HSC活化程度均显著降低,表明mtDNA-先天免疫通路是肝纤维化进展的关键驱动因素^[36-37]。

2.2 加剧代谢紊乱的恶性循环 mtDNA-先天免疫通路不仅是代谢应激(如胰岛素抵抗)的下游效应通路,还能通过多环节反馈调节加重代谢紊乱,形成“代谢紊乱→mtDNA释放→免疫激活→代谢紊乱加重”的恶性循环^[38]。一方面,免疫激活释放的促炎因子(如TNF- α 、

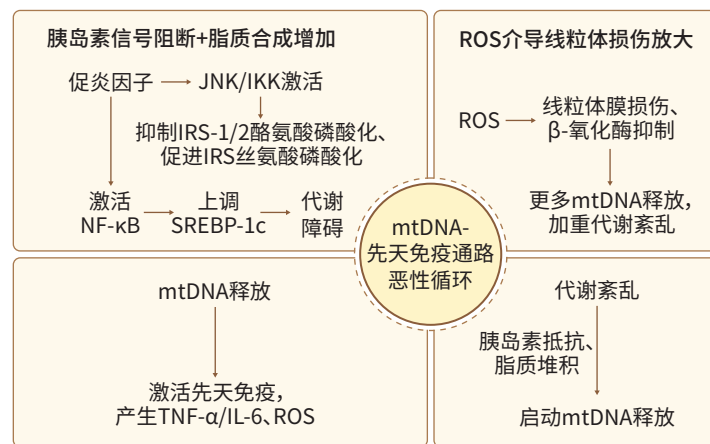
IL-6)通过激活c-Jun氨基端激酶/I κ B激酶,特异性抑制胰岛素受体底物1/2的酪氨酸磷酸化(胰岛素信号激活的关键步骤);同时促进胰岛素受体底物的丝氨酸磷酸化,双重阻断胰岛素信号传导,导致肝脏对糖的摄取与利用障碍,并抑制脂肪分解^[39]。此外,这些促炎因子通过激活转录因子(如NF- κ B),上调肝脏脂质合成相关基因,如固醇调节元件结合蛋白1c的表达,进一步增加肝脏甘油三酯的堆积,加重初始的代谢应激^[40]。另一方面,免疫反应激活产生的ROS形成“线粒体损伤-ROS-代谢紊乱”的次级放大效应:ROS不仅氧化损伤线粒体膜结构,还可抑制线粒体脂肪酸 β -氧化关键酶的活性,降低线粒体对脂肪酸的分解能力,导致脂质在肝细胞内过度堆积,进一步破坏线粒体稳态,促进更多的mtDNA释放,形成代谢与免疫的双向恶化^[3,41]。这种多环节的恶性循环使代谢紊乱与免疫失衡相互驱动、持续加剧,最终推动MAFLD从单纯性脂肪肝向MASH、肝纤维化进展,成为疾病中晚期难以逆转的重要机制(图2)。

3 靶向mtDNA-先天免疫通路干预MAFLD

3.1 药物干预:保护线粒体与调控氧化应激 药物干预以“保护线粒体功能、稳定线粒体结构”为核心目标,从源头上减少mtDNA的异常释放。该策略因作用靶点明确、对全身免疫功能影响较小,具有特异性高、副作用可控的优势^[4]。

线粒体保护剂通过靶向修复线粒体结构与功能、阻断“线粒体损伤→mtDNA释放→先天通路激活”这一链条,从而干预MAFLD进展。近年来,越来越多研究表明,天然药物因具有线粒体保护活性且毒性低、副作用小的优势,成为该领域靶向干预的重要选择^[42]。以白藜芦醇为代表酚类化合物,可通过多途径保护线粒体功能,包括抑制脂肪生成和促进线粒体生物合成。在人肝癌HepG2细胞模型中,白藜芦醇可抑制葡萄糖诱导的脂肪变性,改善线粒体活性,且不影响细胞存活;同时,其能减轻油酸诱导的肝细胞脂质积累,并通过上调过氧化物酶体增殖物激活受体 γ 辅激活因子1 α 的表达促进线粒体生物合成,提升线粒体膜电位,恢复线粒体电子传递链核心基因的表达;此外,还能调控PTEN诱导激酶1与帕金蛋白的水平及比例,维持线粒体动态平衡,从源头减少mtDNA释放,避免激活后续相关免疫通路(如cGAS-STING通路等)。该过程聚焦于线粒体保护以减少mtDNA释放^[42-44]。

此外,以葛根根系活性成分为代表的异黄酮类化合物,在细胞学实验中能直接改善线粒体功能稳态,提



注:mtDNA,线粒体DNA;JNK/IKK,c-Jun氨基端激酶/IκB激酶;IRS,胰岛素受体底物;NF-κB,核因子κB;SREBP-1c,固醇调节元件结合蛋白1c;ROS,活性氧;TNF-α,肿瘤坏死因子α;IL-6,白细胞介素6。

图2 线粒体DNA-先天免疫通路参与的恶性循环

Figure 2 The vicious cycle mediated by the mitochondrial DNA-innate immunity pathway

升线粒体膜电位与三磷酸腺苷生成,减少ROS产生(避免ROS进一步破坏线粒体膜结构);同时,可恢复棕榈酸损伤后的线粒体吞噬功能,通过维持线粒体结构完整性,以减少mtDNA泄漏引起的炎症反应。该研究聚焦于线粒体保护以阻断mtDNA释放,为MAFLD治疗提供了潜在方向^[45-46]。

氧化应激调控剂通过减少ROS的生成或增强细胞的抗氧化能力,间接稳定线粒体结构、减少mtDNA的释放。研究证实,水飞蓟素(主要活性成分为水飞蓟宾)是MAFLD领域研究广泛的氧化应激调控剂,在细胞学实验中通过双重机制发挥作用。(1)抗氧化损伤:上调肝脏谷胱甘肽过氧化物酶、超氧化物歧化酶等抗氧化酶的活性,清除线粒体基质内过量的ROS,避免线粒体膜磷脂被氧化断裂,维持膜结构的完整性。(2)稳定线粒体形态与电位,激活β-联蛋白信号通路,上调线粒体融合蛋白(如视神经萎缩蛋白1)的表达,抑制线粒体碎片化(线粒体分裂过度易导致膜破裂),从而维持线粒体膜电位稳定,降低mtDNA跨膜释放的风险,围绕线粒体保护以减少mtDNA释放^[47-48]。

此外,核转录因子红系2相关因子2(nuclear factor-erythroid 2-related factor 2, Nrf2)是细胞抗氧化应激的核心转录因子,可调控血红素氧合酶1、醌氧化还原酶1等抗氧化酶的表达。有研究发现,萝卜硫素作为天然的Nrf2激活剂,在动物学实验中(以MAFLD小鼠为研究模型)可通过激活Nrf2通路增强肝细胞的抗氧化能力,减轻ROS蓄积,进而减少ROS介导的线粒体膜损伤,降低mtDNA的释放,最终减轻MAFLD小鼠肝脂肪变性、炎症等病理损伤的程度,该研究既涉及线粒体保护,也通过

降低mtDNA释放干预后续病理反应^[49]。

3.2 生活方式干预:改善代谢与线粒体功能 以饮食调整和规律运动为核心的生活方式干预是MAFLD的一线基础治疗手段,通过改善肝脏脂质代谢、减轻氧化应激等代谢紊乱状态,间接抑制mtDNA的异常释放,最终通过改善上游代谢紊乱,间接调控mtDNA-先天免疫轴的过度激活,减轻其介导的肝脏炎症反应^[50]。

饮食调整的核心是通过优化营养结构减少肝脏代谢负担。其中,地中海饮食(富含ω-3多不饱和脂肪酸、可溶性膳食纤维、维生素E等抗氧化物质)的调控作用最为明确。在动物学实验中,ω-3多不饱和脂肪酸可通过抑制肝脏固醇调节元件结合蛋白1c通路减少肝细胞内甘油三酯合成^[51];可溶性膳食纤维(如菊粉)通过调节肠道微生物群减少内毒素入血,间接降低肝脏炎症负荷^[52];维生素E等抗氧化物质可清除过量ROS。三者共同保护线粒体膜结构与呼吸链功能,减少mtDNA释放的风险,该干预过程聚焦于线粒体保护以减少mtDNA释放,为MAFLD患者提供了更精准的饮食干预方向^[53]。

规律运动通过增强线粒体生物合成与脂肪酸氧化能力,改善线粒体结构完整性与功能稳定性,进而减少mtDNA的释放^[54]。动物学实验表明,中等强度有氧运动可激活腺苷酸活化蛋白激酶-过氧化物酶体增殖物激活受体γ辅激活因子1α,后者作为线粒体生物合成的核心转录共激活因子,可促进mtDNA的复制与呼吸链复合物(如复合物I、IV)的表达,增强脂肪酸β的氧化能力,减少脂质在肝细胞内堆积^[55]。同时,细胞学实验证实,运动可通过上调线粒体抗氧化酶的表达,减轻ROS介导的线粒体损伤,有效减少mtDNA介导的后续病理反应。

该干预既聚焦线粒体保护,也通过减少mtDNA释放干预后续反应,成为MAFLD综合管理中安全且有效的非药物干预手段^[56]。

4 小结

mtDNA释放触发的先天免疫机制是MAFLD进展的核心驱动因素,通过“mtDNA释放-模式识别受体激活-促炎因子释放”的病理级联反应,不仅推动肝细胞损伤、MASH及肝纤维化进展,还参与代谢-免疫失衡的恶性循环,进一步加剧疾病的恶化。目前,靶向该通路的干预主要包括药物干预(如水飞蓟素)与生活方式干预(如地中海饮食、有氧运动),部分药物(如水飞蓟素相关制剂)已进入临床应用阶段,在MAFLD等领域展现出良好的应用前景。然而,当前研究处于“单一药物探索、基础机制待深化”的阶段,仍存在mtDNA释放分子机制未明、不同细胞中通路功能差异不清等问题。未来可通过多靶点协同调控、拓展更多药物种类、深入解析分子机制,有望突破当前药物干预不足的瓶颈,为MAFLD尤其是中晚期MASH、肝纤维化患者提供新型、高效的治疗方案,最终改善MAFLD患者的临床预后。

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