线粒体动力学调控在脂肪性肝病中的作用及机制研究进展

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摘要: 脂肪性肝病 (steatotic liver disease, SLD) 是以肝细胞脂质异常积聚为特征的疾病, 主要分为代谢功能障碍相关脂肪性肝病、酒精相关性肝病和代谢与酒精相关脂肪性肝病。多数患者起初为单纯性脂肪肝, 随着病情进展, 逐渐发展为肝炎、肝纤维化和肝硬化。线粒体是高度动态的细胞器, 通过不断地分裂和融合改变线粒体的形态、大小及位置, 此过程被称为线粒体动力学。线粒体动力学失衡会引发线粒体功能障碍, 导致肝脏细胞脂质沉积增多, 同时肝脏细胞的抗氧化防御能力降低, 活性氧积累引发脂质过氧化, 从而造成脂毒性增加和肝损伤。因此, 在脂肪性肝病的进程中, 线粒体动力学扮演重要的角色。本文以线粒体动力学与线粒体自噬、线粒体内质网结构偶联、线粒体依赖性细胞凋亡的关系为切入点, 系统梳理了目前天然化合物通过调控线粒体动力学相关细胞功能改善脂肪性肝病的作用及机制, 以期为天然化合物治疗脂肪性肝病的后续研究及进一步临床开发与应用提供依据和线索。

关键词: 线粒体动力学; 线粒体自噬; 线粒体内质网结构偶联; 线粒体依赖性细胞凋亡; 脂肪性肝病

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Research progress on the role and mechanism of mitochondrial dynamics regulation in steatotic liver disease

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Abstract: Steatotic liver disease (SLD) is a disease characterized by abnormal accumulation of lipids in hepatocytes, which includes metabolic dysfunction-associated steatotic liver disease, alcohol-associated liver disease, and metabolic dysfunction and alcohol-related liver disease. Most patients only have simple liver steatosis at an early stage, which will gradually develop into hepatitis, liver fibrosis, and cirrhosis as the progression of the disease. Mitochondria is a highly dynamic organelle, which changes its morphology, size, and location by continuous division and fusion. This process is known as mitochondrial dynamics. The imbalanced mitochondrial dynamics can cause the dysfunction of mitochondria, leading to increased lipid deposition in liver cells, as well as antioxidant capacity deficient associated reactive oxygen species accumulation and lipid peroxidation, resulting in increased lipotoxicity and liver injury. Therefore, mitochondrial dynamics play an important role in the development of steatotic liver disease. In this review, the relationship between mitochondrial dynamics and mitophagy, mitochondrial-associated endoplasmic reticulum membranes, and mitochondrial-dependent apoptosis in steatotic liver disease were discussed. In addition, the mechanism role of natural compounds in improving steatotic

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liver disease *via* regulating mitochondrial dynamics-related cell functions was also systematically reviewed, aiming to provide the basis and clues for the subsequent investigations and further clinical development and application of natural compounds in the treatment of steatotic liver disease.

Key words: mitochondrial dynamics; mitophagy; mitochondrial-associated endoplasmic reticulum membrane; mitochondria-dependent apoptosis; steatotic liver disease

脂肪性肝病 (steatotic liver disease, SLD) 是以肝细胞脂质异常积聚为特征的慢性肝脏疾病, 主要包括代谢功能障碍相关脂肪性肝病 (metabolic dysfunction-associated steatotic liver disease, MASLD)、酒精相关性肝病 (alcohol-associated liver disease, ALD) 和代谢与酒精相关脂肪性肝病 (metabolic dysfunction and alcohol-related liver disease, MetALD)[1,2]。随着人们生活方式的改变和生活质量的提高, 脂肪性肝病在世界范围内发病率逐年增加。多数患者起初为慢性脂肪肝, 随着疾病的进展, 部分脂肪性肝病可能进一步发展为肝炎、肝纤维化和肝硬化。目前, 脂肪性肝病已经成为影响公众健康的重要因素[3]。

线粒体作为维持肝脏细胞功能的重要细胞器, 参与肝脏能量生成、氧化还原平衡和代谢调节等多个生理过程。其中, 脂肪酸氧化是线粒体的重要能量代谢途径, 能通过氧化磷酸化过程将脂肪酸分解代谢产生的能量转化为三磷酸腺苷 (adenosine triphosphate, ATP), 为机体提供所需能量[4]。然而, 线粒体功能受损会削弱脂肪酸氧化等能量代谢能力, 导致脂肪在肝内蓄积, 从而引发脂肪性肝病。同时在脂肪酸氧化的过程中, 受损线粒体代谢还会产生大量活性氧 (reactive oxygen species, ROS)。过度积累的 ROS 会进一步对线粒体 DNA (mitochondrial genome, mtDNA) 造成损伤, 同时促进受损的 mtDNA 释放到细胞质, 被 Toll 样受体 9 (Toll-like receptor 9, TLR9) 识别, 进而激活核转录因子 kappa B (nuclear factor of kappa B, NF-κB) 信号通路, 增加肿瘤坏死因子 α (tumor necrosis factor alpha, TNFα) 和白细胞介素-6 (interleukin 6, IL-6) 等促炎因子的表达水平[5]。此外, mtDNA 还能够直接激活 NOD 样受体蛋白 3 (NOD-like receptor protein 3, NLRP3) 炎症小体, 诱导 IL-1β 和 IL-18 等促炎因子的释放, 进一步加剧肝脏的炎症反应, 促进脂肪性肝炎的发展[6]。

线粒体是一种处于高度动态的细胞器, 能够通过线粒体动力学的调控对外界刺激做出快速反应, 维持细胞正常功能[7,8]。临床和基础研究均表明, 脂肪性肝病的发生发展与线粒体动力学之间存在密切联系。线粒体动力学紊乱会导致线粒体功能障碍, 使线粒体自噬功能受损[9-11]、促进细胞凋亡[12,13]和炎症信号通路的激活[13]。此外, 线粒体动力学失衡还会减少线粒体与内质网的接触面积并破坏钙稳态, 引发内质网应激, 加重肝细胞损伤和疾病的进展。本文以线粒体动力学与线粒体自噬、线粒体内质网结构偶联 (mitochondrial-associated endoplasmic reticulum membranes, MAMs)、线粒体依赖性细胞凋亡的关系为切入点, 系统梳理了目前线粒体动力学调控在脂肪性肝病中的作用机制, 以及天然化合物通过调控线粒体动力学介导的细胞功能防治脂肪性肝病的机制研究进展, 以期为天然化合物治疗脂肪性肝病的后续研究及进一步临床开发与应用提供线索和依据。

1 线粒体动力学

线粒体动力学是线粒体融合和分裂处于动态平衡的过程, 这一过程能够影响线粒体自噬、MAMs 和线粒体依赖性细胞凋亡等多种细胞功能。因此, 研究线粒体的动态变化对细胞功能的影响, 有助于深入理解线粒体的功能和调节机制。正常生理条件下, 线粒体融合和分裂依赖于多种蛋白的共同调控, 以维持细胞线粒体的动态平衡 (图 1)。线粒体融合能够将功能失调的线粒体与健康的线粒体结合, 中和受损的成分、促进物质交换, 以保持线粒体结构的完整性和线粒体功能的稳定性[14,15]。线粒体分裂则可以选择性地去除受损部分, 保持健康部分的线粒体完好无损, 其在细胞增殖和修复中起关键作用[16,17]。因此, 线粒体动力学对维持线粒体稳态和细胞正常生命活动至关重要。

1.1 线粒体融合 线粒体融合是细胞内重要的生物过程, 涉及线粒体外膜和内膜的融合[18]。线粒体外膜的融合主要受丝裂蛋白 1 (mitofusin-1, MFN1) 和 MFN2 调控。MFN1 和 MFN2 结构相似, 包括 N 端的鸟苷三磷酸酶 (guanosine-triphosphate hydrolase, GTPases) 结构域、七肽重复序列结构域 (HR1 和 HR2), 以及位于 HR1 和 HR2 之间的跨膜结构域。MFN1 和 MFN2 通过两个跨膜结构域锚定在线粒体外膜上, 而 GTPase 结构域和 HR2 结构域则暴露于线粒体外的胞质中[19]。相邻线粒体 MFNs 的 GTPase 和 HR2 结构域间相互作用, 形成 MFNs-MFNs 复合物。随着 GTPase 对 GTP 的水解, 相邻线粒体不断靠近, 最终实现线粒体外膜融合[20]。研究表明, MFN1 缺失会引发线粒体形态碎片

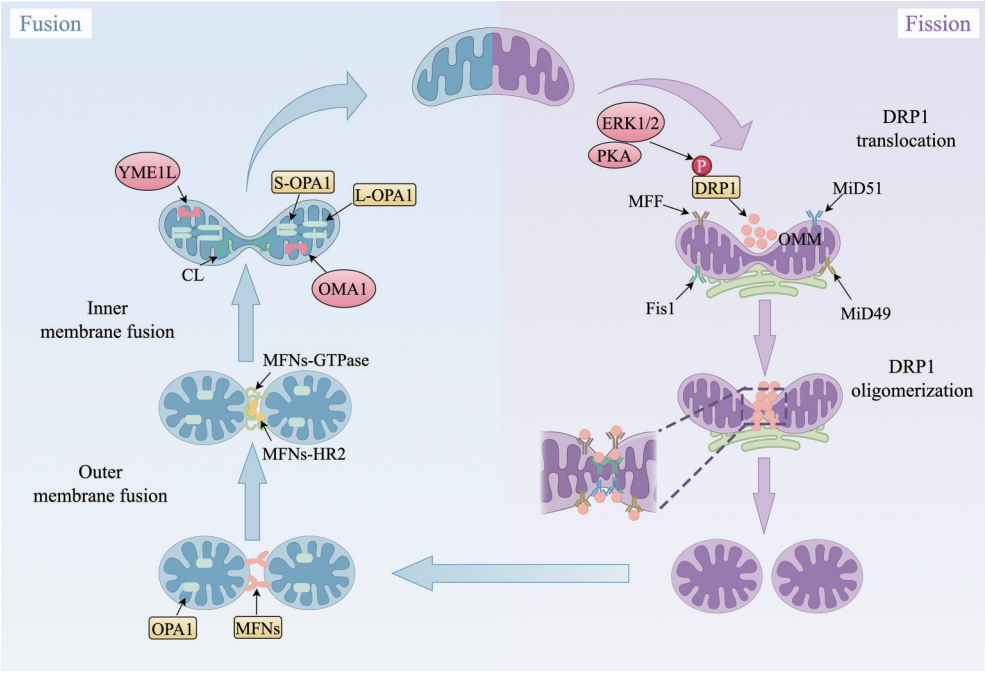


Figure 1 The mechanisms of mitochondrial dynamics. Mitochondrial fusion: Mitochondrial outer membrane fusion is mediated by MFN1 and MFN2. The adjacent extracellular domain of MFNs, HR2, and GTPase, interact with each other to promote mitochondrial outer membrane fusion. Mitochondrial inner membrane fusion depends on OPA1 and CL, which promotes mitochondrial inner membrane fusion by enhancing the interaction of L-OPA1 with CL *via* GTP hydrolysis. Mitochondrial fission: Mitochondrial fission mainly occurs on the site of MAMs. Mitochondrial inner membrane fission is primarily dependent on actin polymerization. Fission of the outer mitochondrial membrane involves the recruitment of DRP1 from the cytoplasm to the outer mitochondrial membrane, where it binds to the membrane interface proteins MFF, Fis1, MiD49, and MiD51 on the outer mitochondrial membrane. Finally, the fission of the outer mitochondrial membrane is completed under the catalysis of DRP1 GTPase activity. MFNs: Mitofusin-1/2; OPA1: Optic atrophy protein 1; GTPase: Guanosine-triphosphate hydrolase; OMA1: Metalloprotease-related protein 1; CL: Cardiolipin; YME1L: YME1 like 1 ATPase; DRP1: Dynamin-related protein 1; PKA: Protein kinase A; ERK1/2: Extracellular-signal regulated kinase 1/2; MFF: Mitochondrial fission factor; Fis1: Mitochondrial fission protein 1; MiD49/51: Mitochondrial dynamic proteins of 49/51; OMM: Outer mitochondrial membrane; MAMs: Mitochondrial-associated endoplasmic reticulum membranes (created with figdraw)

化, 而MFN2缺失则会导致线粒体呈球形或者椭圆形。因此, MFN1和MFN2在线粒体融合过程中具有不同的功能, 线粒体外膜高效融合过程需要MFN1和MFN2的共同参与。线粒体内膜的融合则主要由视神经萎缩蛋白1 (optic atrophy protein 1, OPA1)和心磷脂(cardiolipin, CL)所介导。OPA1作为一种GTPase蛋白, 具有两种长度不同的亚型: 长亚型(L-OPA1)和短亚型(S-OPA1)[21]。L-OPA1锚定在线粒体内膜上, 通过水解GTP介导L-OPA1与CL的相互作用, 促进线粒体内膜融合[22]。此外, L-OPA1在金属蛋白酶1 (metallo-protease-related protein 1, OMA1)和YME1样蛋白酶(YME1 like 1 ATPase, YME1L)的水解作用下可以转变为S-OPA1[23,24]。S-OPA1能进一步促进L-OPA1与CL的结合, 加速线粒体融合网络的形成。而缺乏S-OPA1或缺乏L-OPA1均会抑制线粒体内膜的融合[25]。因此, 线粒体内膜的融合需要L-OPA1和S-OPA1两种亚型的共同参与。

1.2 线粒体分裂 线粒体分裂发生在线粒体与内质网接触部位, 包括线粒体内膜分裂和外膜分裂。线粒体内膜在线粒体外膜之前先进行初始分裂。分裂信号启动后, 内质网中Ca^{2+}浓度升高, 线粒体与内质网的接触时间延长。内质网定位的反向甲酸精2 (inverted formin 2, IFN2)和线粒体内膜上的肌动蛋白成核因子1 (spire type actin nucleation factor 1, SPIRE1)诱导肌动蛋白在线粒体积聚。在肌球蛋白IIA的辅助下, 肌动蛋白聚合, 进而推动线粒体内膜的初始收缩[26]。当内质网中Ca^{2+}浓度达到一定阈值后, Ca^{2+}会从内质网流入线粒体, 导致线粒体内膜上的Ca^{2+}积累, 引发线粒体膜电位降低, 进而促进线粒体内膜局部收缩和分裂[27]。线粒体外膜分裂则主要依赖于动力相关蛋白1 (dynamin-related protein 1, DRP1), 特别是其N端具有高度保守的GTPase结构域[28]。DRP1能通过线粒体膜

衔接蛋白如线粒体分裂因子 (mitochondrial fission factor, MFF)、线粒体分裂蛋白 1 (mitochondrial fission protein 1, Fis1)、线粒体动力蛋白 49 (mitochondrial dynamic proteins of 49, MiD49) 和 MiD51 的介导, 从细胞质被募集到线粒体外膜[29]。多个 DRP1 分子紧密包围线粒体形成环状结构, 依靠其 GTPase 活性水解 GTP, 促进线粒体外膜的断裂[5]。研究表明, DRP1 的磷酸化状态在线粒体分裂调控过程中起关键的作用。蛋白激酶 A (protein kinase A, PKA) 可以介导 DRP1 丝氨酸 637 位点的磷酸化, 降低 DRP1 的 GTPase 活性, 抑制线粒体分裂[30]。而细胞周期蛋白依赖激酶 1 (cyclin-dependent kinase 1, CDK1) 和细胞外信号调节激酶 1/2 (extracellular-signal regulated kinase 1/2, ERK1/2) 则能够通过磷酸化 DRP1 的丝氨酸 616 位点, 激活 DRP1 的 GTPase 活性, 促进线粒体分裂[31,32]。

1.3 线粒体动力学与肝脏细胞功能 肝脏是人体重要的代谢和解毒器官, 由肝细胞、内皮细胞、巨噬细胞等多种类型细胞组成。线粒体作为肝脏中细胞能量代谢的核心, 能够通过氧化磷酸化将糖类和脂质等氧化生成 ATP, 为肝脏的高能量需求提供支持。此外, 肝脏细胞中线粒体物质代谢过程还会产生 ROS, 过量的 ROS 会导致氧化应激和 mtDNA 损伤, 引发肝脏细胞线粒体功能障碍。有研究表明, 在众多肝脏细胞中肝细胞线粒体功能障碍是脂肪性肝病发生发展的重要驱动因素[33]。肝细胞中功能异常的线粒体能够通过释放多种炎症介质诱导 Kuffer 细胞中 NF-κB 等信号通路的激活, 促进 TNFα、IL-6 等促炎因子的释放, 并进一步诱导和招募单核巨噬细胞、中性粒细胞等免疫细胞的浸润和活化, 加剧脂肪性肝炎的发展[34]。线粒体动力学作为线粒体功能的基本调控途径, 是维持细胞结构和功能稳态的核心。线粒体动力学失衡会引发线粒体功能失调, 导致肝脏细胞脂质沉积增加, 同时肝脏细胞的抗氧化防御能力降低, ROS 积累引发脂质过氧化, 从而造成脂毒性增加和肝损伤[35]。此外, 线粒体动力学紊乱还会通过促进细胞色素 C (cytochrome C, CytC) 或 mtDNA 的释放, 引发细胞凋亡和炎症反应, 进一步加重肝损伤。事实上, 线粒体动力学不仅影响细胞物质代谢和凋亡, 还能够通过调控线粒体自噬、MAMs 等细胞功能来维持肝脏细胞的正常结构及生理功能 (图 2)[36]。

2 线粒体动力学调控在脂肪性肝病中的作用

2.1 线粒体动力学与线粒体自噬 线粒体自噬是一种选择性的自噬过程, 通过特定的机制识别并清除受损线粒体来维持线粒体的质量和数量平衡, 从而确保细胞的正常生理功能和稳态。研究表明, 线粒体动力学的改变对线粒体自噬的启动必不可少。受损的线粒体需要线粒体分裂蛋白 DRP1 参与, 将线粒体分裂成合适大小的线粒体片段, 以便通过线粒体自噬清除[37]。

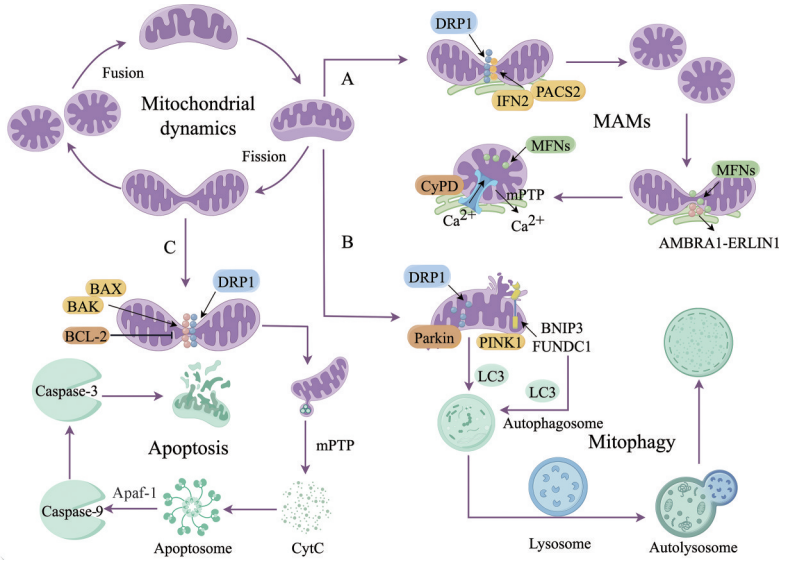


Figure 2 The regulatory function of mitochondrial dynamics in MAMs, mitophagy and mitochondrial-dependent apoptosis. A: The association between mitochondrial dynamics and MAMs regulation; B: Mitochondrial dynamics regulates mitophagy; C: Mitochondrial dynamics regulates mitochondria-dependent apoptosis. IFN2: Inverted formin 2; PACS2: Phosphofurin acidic cluster sorting protein 2; CyPD: Cyclophilin D; mPTP: Mitochondrial permeability transition pore; BNIP3: BCL-2 interacting protein 3; FUNDC1: FUN14 domain containing 1; PINK1: PTEN-induced putative kinase 1; LC3: Microtubule-associated protein 1 light chain 3; BCL-2: B-cell lymphoma-2; BAK: BCL-2 antagonist; CytC: Cytochrome C; Apaf-1: Apoptotic protease activating factor-1; Caspase-3/9: Cysteinyl aspartate specific proteinase 3/9 (created with figdraw)

线粒体自噬过程主要受到PINK1/Parkin依赖性途径和非泛素依赖性途径的调控。在PINK1/Parkin依赖性途径中, 全长PINK1通过TOM/TIM复合物转运至健康线粒体, 随后被线粒体内膜的PARL切割并释放至细胞质[38]。胞质中的PINK1进一步被泛素−蛋白酶体系统 (ubiquitin-proteasome system, UPS) 降解, 以维持正常线粒体中PINK1的低水平[39]。然而, 当线粒体受损时, PINK1向线粒体内部转运受阻, 因而不会被PARL识别切割, 导致PINK1在线粒体外膜稳定和积累[38]。稳定的PINK1能通过自磷酸化激活其自身的激酶活性, 同时招募并促进E3泛素连接酶Parkin的活化。激活的Parkin进一步对线粒体外膜中的多功能蛋白电压依赖性阴离子通道1 (voltage dependent anion channel 1, VDAC1) 和MFN1/2等进行泛素化修饰[40], 并促进特异性的自噬受体蛋白如螯合体1 (sequestosome 1, SQSTM1/p62)、视神经蛋白 (optineurin, OPTN) 与上述泛素化蛋白结合, 从而被招募到受损的线粒体上与微管相关蛋白1轻链3 (microtubule-associated protein 1 light chain 3, LC3) 结合, 促进自噬体对受损线粒体的包裹。最终, 通过自噬溶酶体途径将受损的线粒体降解[41]。最近研究发现, 线粒体分裂过程蛋白1 (mitochondrial process 1, MTFP1) 可以抑制OPA1的寡聚化, 并增强DRP1向线粒体外膜的募集, 促进线粒体分裂, 从而形成富含MTFP1的小线粒体。同时, MTFP1还可以作为一种线粒体自噬受体, 与LC3相互作用, 通过PINK1/Parkin依赖性线粒体自噬途径清除功能失调的小线粒体[42,43]。在非泛素依赖性途径中, 线粒体自噬的发生能够独立于PINK1, 直接通过自噬受体如BCL-2相互作用蛋白3 (BCL-2 interacting protein 3, BNIP3) 和FUN14结构域包含1 (FUN14 domain containing 1, FUNDC1) 与LC3蛋白结合形成自噬体, 进而包裹受损的线粒体, 启动线粒体自噬[44]。研究发现, 线粒体融合蛋白OPA1通过其Lys70残基与FUNDC1相互作用, 抑制线粒体分裂和线粒体自噬。而在线粒体应激条件下, FUNDC1发生去磷酸化, 导致其与OPA1解离, 并增强DRP1向线粒体外膜的募集, 从而促进线粒体分裂和线粒体自噬的启动[45]。

大量研究表明, 线粒体动力学失衡会破坏线粒体内稳态, 造成线粒体功能障碍, 使线粒体自噬无法正常发挥功能, 从而导致脂肪性肝病的发生发展。一方面, 线粒体动力学介导的线粒体自噬启动不足, 使受损线粒体异常积累, 进而加重肝脏损伤。如在脂肪性肝病的大鼠和小鼠肝脏中, 线粒体分裂蛋白水平降低, 线粒体动力学紊乱, 导致线粒体自噬相关蛋白PINK1、Parkin的表达减少, 线粒体自噬受损[11,46]。此外, 在DRP1敲除小鼠的肝脏中, 线粒体过度融合导致巨大线粒体增多[47], 造成线粒体自噬无法正常激活来清除异常线粒体[48,49]。受损线粒体代谢产生大量的ROS, 对mtDNA造成损伤。受损的mtDNA能够通过线粒体通透性转换孔 (mitochondrial permeability transition pore, mPTP) 释放到胞质中, 激活环状GMP-AMP合酶−干扰素基因刺激因子 (cyclic GMP-AMP synthase-stimulator of interferon genes, cGAS-STING) 信号通路, 引发炎症反应, 进一步加重脂肪性肝炎[47,50]。而过表达DRP1则可以挽救因分裂不足引起的线粒体自噬缺陷, 降解和清除受损的线粒体, 减少mtDNA的释放, 从而减轻炎症反应[51]。另一方面, 在进行性的脂肪性肝病如脂肪性肝炎和肝纤维化中, 也存在线粒体自噬的过度激活。线粒体自噬的过度激活会促进NLRP3炎症小体介导的IL-1β释放, 进一步加剧脂肪性肝炎的发展[52]。此外, NLRP3炎症小体的激活还会诱导肝星状细胞的活化, 促进肝纤维化的发生。而通过调节线粒体动力学可以有效减轻线粒体自噬的过度激活, 抑制肝星状细胞的增殖和纤维化, 从而延缓脂肪性肝病的进展[53]。

2.2 线粒体动力学与MAMs MAMs是指线粒体外膜与内质网膜之间形成的紧密物理连接, 可以促进线粒体与内质网之间的物质交换和信号转导, 维持细胞稳态。MAMs根据接触面积可以分为3种: 内质网小管接触覆盖线粒体表面10%、内质网小管接触覆盖线粒体表面50%、内质网小管完全包裹整个线粒体[32,54]。研究表明, 线粒体动力学与MAMs之间存在复杂的相互作用。内质网小管与线粒体紧密接触确定线粒体外膜收缩位点后, MAMs相关蛋白如磷酸呋喃酸性簇分选蛋白2 (phosphofurin acidic cluster sorting protein 2, PACS2)、IFN2、FUNDC1等参与线粒体分裂蛋白DRP1的募集, 促进线粒体在收缩位点处分裂[55-57]。而存在于内质网膜中的MFN2则能够通过与线粒体外膜上的MFN1或MFN2相互作用, 促进内质网与线粒体之间的接触[58]。此外, 线粒体融合相关蛋白MFN2也可以与其他MAMs组分如AMBRA1-ERLIN1复合物相互作用[59], 控制内质网与线粒体的间隙距离, 维持细胞间物质交换和蛋白质相互作用[60]。研究表明, MAMs可以通过维持Ca^{2+}转运平衡, 防止内质网应激。内质网作为Ca^{2+}主要的储存库, 其中高浓度Ca^{2+}从内质网转运到线粒体需要依赖于MAMs的介导。内质网与线粒体之间的距离和MAMs相关蛋白组成均会影响Ca^{2+}的转运效率。研究发现, 内质网与线粒体间隙距离适当增加, 可以提高Ca^{2+}的转运效率[61]。而线粒体外膜蛋白VDAC和线粒体内膜钙单向转运蛋白 (mitochon-

drial calcium uniporter, MCU) 可以与三磷酸肌醇受体 (inositol 1,4,5-triphate receptor, IP3R) 结合形成复合物, 共同调节 Ca^{2+} 转运信号。此外, 线粒体融合蛋白 MFNs 和 MAMs 相关蛋白亲环素 D (cyclophilin D, CyPD) 也能够通过影响 IP3R 与 VDAC 的相互作用, 促进线粒体对 Ca^{2+} 的摄取[27]。当线粒体中的 Ca^{2+} 积累到一定浓度, 则会通过 mPTP 将 Ca^{2+} 释放到胞质中, 使线粒体中 Ca^{2+} 的摄取与外排相当, 维持 Ca^{2+} 转运平衡, 防止内质网应激的发生。

线粒体动力学介导的 MAMs 与脂肪性肝病的发生发展密切相关。MAMs 的接触面积和间隙距离出现偏差, 会导致线粒体功能障碍, 破坏细胞稳态, 引发脂质代谢紊乱[62]。CDP-甘油二酯合酶 2 (CDP-diacylglycerol synthase 2, CDS2) 能够在 MAMs 中富集, 而肝脏特异性缺乏 CDS2 会导致 MFN1 和 MFN2 蛋白水平降低, 并且改变线粒体与内质网的间隙距离, 损害线粒体功能, 抑制其脂肪酸氧化作用, 进而引起肝脏脂肪变性和炎症反应[63]。而过表达 MFN2 则能够恢复 MAMs 的接触面积, 改善内质网与线粒体之间的相互作用, 维持线粒体正常形态和功能[64]。最新研究发现, MICOS 复合物的核心成分 Mic19 能够通过参与 EMC2-SLC25A46-Mic19 信号轴来调节内质网与线粒体的接触。在肝脏特异性 Mic19 敲除小鼠中, 内质网与线粒体接触面积减少, 导致线粒体结构异常, 从而损害小鼠肝脏线粒体脂肪酸氧化和脂质代谢。而过表达 Mic19 能够明显增加内质网与线粒体的接触面积, 改善肝脏脂质代谢紊乱[65]。此外, 线粒体融合分裂失衡, 会导致 MAMs 结构受损和 Ca^{2+} 平衡紊乱, 诱发与脂肪性肝损伤相关的内质网应激[66]。如线粒体融合蛋白 MFN2 表达降低, 会增加 VDAC 与 IP3R 相互作用, 进一步导致内质网与线粒体间隙中 Ca^{2+} 的水平升高, MCU 通道持续性开放, 使线粒体中 Ca^{2+} 超载, 引发内质网应激, 从而加重高脂饮食诱导的肝脏脂肪变性。而使用 MCU 抑制剂则能够有效阻断 MCU 通道的开放, 降低线粒体中 Ca^{2+} 的浓度, 减轻内质网应激相关肝脏损伤[67]。研究发现, 沉默 MFN2[68] 或敲除 CyPD[69] 均会损害内质网形态, 减弱内质网与线粒体之间的相互作用, 抑制 Ca^{2+} 从内质网向线粒体的转运, 从而导致线粒体中 Ca^{2+} 平衡紊乱, 内质网应激相关蛋白如 C/EBP 同源蛋白 (C/EBP-homologous protein, CHOP) 和转录因子 4 (transcription factor 4, ATF4) 的表达升高, 并损害线粒体 RNA 的表达, 导致肝脏线粒体功能障碍, 加速脂肪性肝炎的进展[70,71]。

2.3 线粒体动力学与线粒体依赖性细胞凋亡 线粒体依赖性细胞凋亡是一种程序性的细胞死亡, 主要受到 B 淋巴细胞瘤-2 (B-cell lymphoma-2, BCL-2) 家族和含半胱氨酸的天冬氨酸蛋白水解酶 (cysteinyl aspartate specific proteinase, caspase) 家族蛋白调控。其中, BCL-2 家族包括促凋亡蛋白 BAX、BAK 和抗凋亡蛋白 BCL-2 等。细胞受到刺激或损伤后, 促凋亡蛋白 BAX 在线粒体外膜处聚集并被活化, 线粒体通透性发生改变, 导致 mPTP 开放, 促使 CytC 和其他凋亡因子释放到细胞质中[72]。释放到胞质中的 CytC 与凋亡蛋白酶因子 1 (apoptotic protease activating factor-1, Apaf-1) 结合, 形成凋亡小体, 并启动 caspase-9 的二聚化, 进一步激活 caspase-3 和 caspase-7, 促进 caspase 介导的细胞内容物分解, 从而导致细胞凋亡的发生[73]。有研究发现, 在细胞凋亡的过程中, 线粒体分裂蛋白 DRP1 和线粒体融合蛋白 MFN2 与促凋亡蛋白 BAX 在线粒体上存在共定位[74], 表明线粒体动力学与线粒体依赖性细胞凋亡存在潜在的联系。进一步研究发现, 线粒体分裂本身不会直接诱导细胞凋亡, 但 DRP1 可以通过促进线粒体膜的半融合状态诱导 BAX 蛋白的聚集, 促进 CytC 的释放, 启动细胞凋亡[75,76]。此外, BAX 的 N 端结构域可以直接特异性地与 DRP1 相互作用, 形成同源二聚体复合物, 影响 BAX 的活性[75]。敲低 DRP1 或使用 DRP1 抑制剂 Mdivi-1 处理可以抑制线粒体分裂, 降低 BAX 活性, 减少 CytC 的释放, 进而抑制 caspase 的激活, 阻碍细胞凋亡的发生[77,78]。而使用星形孢菌素激活 DRP1, 则能够促进 BAX 聚集和激活, 加剧细胞凋亡[79]。研究还发现, 线粒体融合蛋白 OPA1 缺失或 MFNs 的沉默会引发线粒体嵴结构受损, 促使 CytC 从嵴向膜间隙的释放增多, 导致细胞凋亡的易感性增加, 而恢复线粒体融合则能够抑制 BAX 的激活和 CytC 的释放, 减少细胞凋亡[74]。

在脂肪变性的肝脏中, 抗氧化酶减少, 脂质过氧化产物丙二醛和 4-羟基壬烯醛增加, 会导致线粒体通透性发生改变, 从而启动线粒体依赖性细胞凋亡途径[80]。在细胞凋亡发生过程中, 线粒体成分和代谢产物, 如 mtDNA 和 ROS 会大量积累, 并促进炎症反应, 从而加速脂肪性肝炎的发展。此外, 受损的肝细胞还可以通过凋亡小体和细胞间通讯直接或间接地促进肝星状细胞活化, 进而加剧脂肪性肝炎向肝纤维化、肝硬化甚至肝癌的发展[81]。研究发现, 在脂质蓄积肝细胞模型中, 线粒体融合蛋白 MFN1 的表达水平显著降低, 促进线粒体分裂, 使 mPTP 开放, 从而增加 CytC 的释放, 启动细胞凋亡。而使用 mPTP 抑制剂环孢素 A 处理后, mPTP 开放能力减弱, CytC 释放减少, 可明显抑制线粒体过度分裂引发的细胞凋亡[82]。此外, 有报道在脂肪性肝炎的肝脏组织中存在着蛋白酪氨酸磷酸酶 1B

(protein tyrosine phosphatase 1B, PTP1B) 及线粒体分裂相关蛋白DRP1的表达上调, 导致BAX在线粒体外膜被募集并激活, 促进mPTP的开放和CytC释放[83]。而抑制PTP1B蛋白表达可以显著减弱线粒体分裂, 减少线粒体外膜上DRP1和BAX的结合, 从而抑制脂质积累诱导的细胞凋亡[84]。

3 天然化合物调控线粒体动力学相关途径改善脂肪性肝病

3.1 线粒体动力学调控介导的线粒体自噬 天然化合物可以通过调控线粒体动力学使线粒体自噬正常发挥功能来改善脂肪性肝病。一方面, 天然化合物通过调控线粒体动力学启动线粒体自噬, 清除受损的线粒体, 维持肝脏细胞正常生理功能。槲皮素是一种广泛存在于各种植物花和叶中的天然类黄酮类化合物, 具有抗炎和抗氧化的作用[85]。槲皮素可以通过恢复DRP1和MFNs的蛋白表达水平维持线粒体动力学平衡, 并上调沉默信息调节因子1 (silent information regulator 1, SIRT1) 的蛋白表达来增强线粒体自噬关键调控因子PINK1和Parkin的表达, 从而激活线粒体自噬, 清除受损线粒体, 进而有效降低细胞内ROS的水平, 减轻氧化应激诱导的线粒体损伤[86]。白藜芦醇是一种从葡萄中提取出来的非黄酮类多酚化合物, 具有较强的抗氧化的活性。有研究表明, 辅酶Q (coenzyme Q, CoQ) 作为一种内源性亲脂抗氧化剂, 不仅可以保护细胞膜脂质免受氧化, 还能与细胞膜中的α-生育酚和细胞内外的抗坏血酸共同作用维持氧化还原循环, 以保持各自的抗氧化活性[87]。在肝脏脂肪变性的发展过程中, CoQ的水平降低。而白藜芦醇能够通过促进DRP1蛋白表达上调CoQ相关基因的表达水平和CoQ依赖性氧化还原酶活性, 提高线粒体的抗氧化能力, 并通过诱导Parkin和线粒体自噬受体BNIP3和FUNDC1等蛋白的表达水平, 激活线粒体自噬, 改善线粒体功能, 从而降低高脂饮食诱导脂质积累, 改善肝脏脂肪变性[88]。另一方面, 天然化合物还可以通过调控线粒体动力学抑制线粒体自噬的过度激活, 改善线粒体功能, 防止ROS过度积累, 进而维持肝脏细胞稳态。研究发现, 岩藻多糖是一种存在于褐藻细胞质基质中的水溶性酸性杂多糖, 其能够恢复DRP1和MFN2的蛋白表达水平, 维持线粒体动力学平衡。其还通过抑制PINK1/Parkin依赖性线粒体自噬的过度激活, 恢复线粒体功能, 减少受损线粒体的积累, 减轻酒精诱导的氧化应激, 从而改善肝脏脂质代谢紊乱[80]。阿福豆苷是从鱼腥草中提取分离出的一种黄酮醇糖苷类化合物[89], 可以提高DRP1表达水平并降低MFN2表达水平, 通过调节线粒体分裂和融合, 降低线粒体自噬相关蛋白PINK1、Parkin的水平, 防止线粒体自噬过度激活造成的线粒体功能紊乱, 从而减轻线粒体损伤, 延缓脂肪性肝病的进展[90]。

3.2 线粒体动力学介导的MAMs 研究表明, 线粒体动力学调控的MAMs可以通过增加线粒体与内质网接触面积以及维持线粒体内Ca^{2+}平衡, 抑制内质网应激, 同时MAMs还能够参与脂质合成、运输和代谢, 对脂肪性肝病的进展具有重要的调节作用。最近研究发现, 邻苯二甲酸二 (2-乙基己基) 酯 (DEHP) 会导致肝脏线粒体动力学失衡, 使MAMs结构受损, 引发内质网应激, 并扰乱胆固醇代谢, 加速肝损伤和纤维化[91]。番茄红素是一种广泛存在于石榴、番茄中的脂肪族类胡萝卜素[92], 其能够缓解DEHP引起的线粒体和内质网结构损伤, 通过上调线粒体分裂蛋白DRP1水平, 调节线粒体动力学平衡, 从而增加线粒体与内质网的接触面积, 促进脂质代谢, 改善肝脏组织的病理损伤情况[93]。虾青素是来源于虾和鲑鱼中一种黄酮类胡萝卜素化合物[94]。研究表明, 虾青素处理可以改善酒精诱导的线粒体功能障碍, 减轻氧化应激、脂质过氧化。Wu等[95]研究发现, 虾青素可以通过调节线粒体动态平衡来抑制mtDNA向线粒体外释放, 从而改善线粒体的功能, 抑制内质网应激, 减少肝脏中的脂质积累。具体而言, 虾青素主要通过促进线粒体融合相关蛋白OPA1、MFN1和MFN2的表达, 增加MAMs中线粒体与内质网的接触面积。同时降低IPR3与VDAC的相互作用, 抑制MCU通道的持续性开放, 减少Ca^{2+}由内质网向线粒体的转运, 恢复线粒体内Ca^{2+}稳态。此外, 虾青素还可以促进mPTP的开放, 使线粒体中超载的Ca^{2+}释放到胞质中, 减轻线粒体内Ca^{2+}的积累, 进而维持Ca^{2+}平衡[96]。另外, 虾青素还能抑制内质网应激相关蛋白CHOP、ATF4的表达水平, 抑制Ca^{2+}从内质网流向线粒体, 维持Ca^{2+}稳态, 并减少线粒体ROS的产生, 维持线粒体氧化还原平衡, 降低氧化应激, 从而有效改善肝脏脂质过氧化状况[97,98]。

3.3 线粒体动力学介导的线粒体依赖性细胞凋亡 近期研究发现, 天然化合物也能够通过调节线粒体依赖性细胞凋亡改善脂肪性肝病。水飞蓟素是从菊科植物水飞蓟种子中提取分离出来的天然黄酮木脂素类化合物[99], 其主要活性成分水飞蓟宾能通过调节线粒体分裂和融合的动态平衡来降低促凋亡蛋白BAX的活性, 抑制caspase-3的切割, 并且增加抗凋亡蛋白BCL-2的表达水平, 从而减少细胞凋亡的发生[79]。杨梅素是从杨梅树皮和叶中提取出来的天然黄酮醇类化合物[100], 其可以通过调控线粒体的分裂融合, 抑制mPTP开放, 减少CytC的释放。研究表明, 杨梅素与caspase-3酶学

活性位点具有较强的结合亲和力, 能抑制 caspase-3 的激活, 从而减轻细胞凋亡[101]。鼠尾草酚是来源于唇形科植物鼠尾草的一种二萜类化合物[102], 其能够通过调控线粒体动力学抑制细胞凋亡来缓解高脂饮食诱导的肝脏脂肪变性。研究发现, 鼠尾草酚可以降低 DRP1 的表达, 减少 BAX 的积聚, 从而抑制 caspase-3 的切割和激活, 减轻细胞凋亡。此外, 鼠尾草酚还可以抑制 ROS 过度生成, 改善肝脏脂质蓄积, 从而有效减缓脂肪性肝病的进展[103]。研究还发现, 岩藻多糖[80]和槲皮素[104]也能够通过降低 DRP1 的表达来抑制 BAX 在线粒体外膜的积聚和活化, 从而减少 CytC 向细胞质的释放, 降低 caspase-3 的激活, 有效减轻乙醇诱导的氧化应激和细胞凋亡。

4 总结与展望

综上, 线粒体动力学在脂肪性肝病的发生发展过程中发挥着重要的作用, 肝脏细胞中的线粒体通过持续地分裂和融合来维持线粒体动态平衡, 调节线粒体功能, 维持细胞稳态, 并能够通过调控线粒体自噬、MAMs 及线粒体依赖性细胞凋亡等细胞功能影响肝脏细胞的生理病理状态。最近研究表明, 线粒体转移作为一种新型的细胞间通讯方式, 其转移过程和功能的发挥与线粒体分裂融合也存在着一定的联系[105]。促进肝脏细胞间的线粒体转移能够改善受损细胞中的氧化应激、脂质蓄积等情况, 减轻脂肪性肝病及肝纤维化的发展[106-108]。但线粒体动力学在细胞间线粒体转移中的具体作用, 以及能否通过调控线粒体动力学来影响线粒体转移改善脂肪性肝病目前仍不明确。未来进一步探究线粒体动力学与细胞间线粒体转移的关系, 可能为脂肪性肝病的发病机制研究和相关药物开发提供新的思路。此外, 当前脂肪性肝病中线粒体动力学调控研究主要集中于肝实质细胞, 未来针对脂肪性肝病中相关免疫细胞线粒体动力学功能的研究, 可能是揭示该类肝脏疾病分子调控机制的另一重要方向。

当前研究表明, 多种食物来源的天然化合物能够通过调控线粒体动力学介导的细胞功能改善脂肪性肝病。在作用机制上, 天然化合物主要通过调控线粒体动力学介导的线粒体自噬、MAMs、线粒体依赖性细胞凋亡等方面, 发挥改善脂肪性肝病的药效机制(表 1)[79,80,86,88,90,93,95-98,101,103,104]。如白藜芦醇和槲皮素均可以通过调节线粒体动力学平衡激活线粒体自噬, 清除受损线粒体; 虾青素和番茄红素则能够通过增加线粒体内质网接触面积, 促进 Ca^{2+} 转运, 维持线粒体内钙稳态, 减轻内质网应激; 杨梅素、水飞蓟宾、鼠尾草酚可以通过抑制线粒体分裂蛋白 DRP1 的表达来减少 BAX 在线粒体外膜的积聚和激活, 进而降低 CytC 的释放, 抑制 caspase-3 的激活, 减轻肝细胞凋亡。

然而, 尽管目前有关天然化合物通过线粒体动力学调控改善脂肪性肝病的研究在不断推进, 但仍存在很多的局限。研究发现, 多种天然化合物均可以通过调控线粒体动力学介导的线粒体自噬改善脂肪性肝病, 但对线粒体自噬作用有着明显的差别。如槲皮素和白藜芦醇通过调控线粒体动力学启动线粒体自噬, 来清除脂肪变性肝脏中受损的线粒体, 避免受损线粒体过度积累导致的线粒体功能障碍。而岩藻多糖和阿福豆苷则通过调控线粒体动力学抑制线粒体自噬的过度激活, 维持细胞稳态。因此, 对于天然化合物通过线粒体动力学介导的线粒体自噬改善脂肪性肝病的具体药效作用机制仍需结合脂肪性肝病病理的不同阶段特征进一步分析研究, 以确定不同化合物的有效干预阶段。

研究发现, 槲皮素和岩藻多糖不仅可以通过调控线粒体动力学影响线粒体自噬, 还可以通过降低 DRP1 的活性来抑制线粒体依赖性细胞凋亡的发生, 从而减缓脂肪性肝病的进展。因此, 脂肪性肝病的治疗研究还应充分发挥天然化合物多靶点、多通路、多途径的优势, 充分挖掘其分子作用机制网络, 以实现对其改善脂肪性肝病机制的充分揭示。脂肪性肝病作为一种慢性肝病, 患者需要长期服药, 因此药物的安全性、

Table 1 Natural products regulate mitochondrial dynamics to ameliorate steatotic liver disease

Function of mitochondrial dynamics regulation	Natural product	Regulated molecule	Reference
Mitophagy	Fucoidan	PINK1, Parkin	[80]
	Quercetin	PINK1, Parkin	[86]
	Resveratrol	Parkin, BNIP3, FUNDC1	[88]
	Afzelin	PINK1, Parkin	[90]
MAMs	Astaxanthin	IRP3, VDAC, MCU, CHOP, ATF4	[95-98]
	Lycopene		[93]
Mitochondrial-dependent apoptosis	Fucoidan	BAX, CytC, caspase-3	[80]
	Silibinin	BAX, caspase-3, BCL-2	[79]
	Quercetin	BAX, CytC, caspase-3	[104]
	Myricetin	CytC, caspase-3	[101]
	Carnosol	BAX, caspase-3	[103]

有效性值得关注。本文中总结的改善脂肪性肝病的天然化合物, 如番茄红素、白藜芦醇、杨梅素等主要以食品来源为主, 具有来源广泛、安全性高等特点, 可作为食品来源补充剂或替代治疗药物用于改善脂肪性肝病。对此类化合物在调控线粒体动力学作用机制的深入研究和分析将为今后脂肪性肝病的预防和长期用药提供新的潜在药物和临床干预途径。

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利益冲突: 作者声明本文不存在任何利益冲突。

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