·综述·

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线粒体功能紊乱在代谢相关脂肪性肝病中的作用机制及中医药干预研究现状

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摘要：代谢相关脂肪性肝病（MAFLD）是一种与代谢紊乱有关的慢性肝病，其发病与肝细胞内脂肪大量堆积引起的脂毒性密切相关。近年研究表明，线粒体功能紊乱是MAFLD发病的重要机制，涉及线粒体氧化应激、线粒体自噬异常、线粒体凋亡异常和线粒体脂质代谢异常等一系列病理变化。中医药基于整体观念和辨证论治两大基本特点，在MAFLD的防治中发挥重要作用。本文对线粒体功能紊乱在MAFLD各病理过程中的作用及中医药的干预效应进行综述，以期从线粒体功能角度为中医药防治MAFLD提供新的思路与方法。

关键词：代谢相关脂肪性肝病；线粒体；中医药疗法

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Mechanism of action of mitochondrial dysfunction in metabolic associated fatty liver disease and the current status of research on traditional Chinese medicine

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Abstract: Metabolic associated fatty liver disease (MAFLD) is a chronic liver disease closely associated with metabolic disorders, and the onset of MAFLD is associated with lipotoxicity caused by the accumulation of a large amount of fat in hepatocytes. Recent studies have shown that mitochondrial dysfunction is an important mechanism for the development of MAFLD, involving a series of pathological changes including mitochondrial oxidative stress, abnormal mitochondrial autophagy, abnormal mitochondrial apoptosis, and abnormal mitochondrial lipid metabolism. Based on the two characteristics of holistic view and syndrome differentiation-based treatment, traditional Chinese medicine (TCM) plays an important role in the prevention and treatment of MAFLD. This article reviews the role of mitochondrial dysfunction in various pathological processes of MAFLD and the intervention effect of TCM, in order to provide new ideas and methods for TCM in the prevention and treatment of MAFLD from the perspective of mitochondrial function.

Key words: Metabolic Associated Fatty Liver Disease; Mitochondria; Traditional Chinese Medicine Therapy

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代谢相关脂肪性肝病(metabolic associated fatty liver disease, MAFLD)是指在排除过量酒精摄入及药物性肝损伤的情况下,5%以上的肝细胞出现脂肪过度沉积、由代谢综合征引发肝脏炎性损伤的临床病理综合征[1]。截至2020年,随着肥胖和2型糖尿病患者在全球范围内的大幅增长,MAFLD的全球患病率已高达25%,成为全球最常见的慢性肝脏疾病之一[2]。线粒体被称为细胞的"能量工厂",参与腺嘌呤核苷三磷酸(adenosine triphosphate, ATP)合成、脂肪酸β-氧化、活性氧(reactive oxygen species, ROS)生成和细胞凋亡等多种生理过程。高脂饮食会诱发线粒体功能紊乱,主要表现为生物合成减少、脂肪酸β氧化受阻、细胞凋亡异常及自噬功能障碍等,进而促使肝细胞内脂质代谢失衡,促进脂质沉积和炎症反应[3-4]。线粒体生物合成主要由过氧化物酶体增殖物激活受体γ共激活因子1α(peroxisome proliferator activated receptor-γ co-activator-1α, PGC-1α)触发,通过核呼吸因子(nuclear respiratory factor, NRF)/线粒体转录因子A(mitochondrial transcription factor A, TFAM)驱动线粒体DNA(mitochon-drial DNA, mtDNA)复制和核基因表达,而PGC-1α过表达可增加线粒体生物合成,增强脂质氧化分解能力,从而降低MAFLD肝脏脂质蓄积[5]。研究表明,改善紊乱的线粒体功能可减轻MAFLD肝脏脂毒性及炎性损伤,表明线粒体功能紊乱是其重要发病机制[6]。因此,关于线粒体功能障碍的研究,有望成为防治MAFLD的新靶点。中医药凭借其多活性组分、多靶点、多途径的作用特点,在防治MAFLD方面具有独特优势。本文系统综述线粒体功能紊乱在MAFLD发展中的作用机制,并总结中医药调控线粒体功能紊乱对MAFLD的干预效应,以期为中医药防治MAFLD提供新的方向与策略。

1 线粒体功能紊乱在MAFLD中的相关机制

1.1 氧化应激 氧化应激是导致MAFLD肝损伤和疾病进展的主要因素之一,其中线粒体氧化应激被认为是肝脏发生炎症的主要机制之一[7-8]。在MAFLD晚期阶段,肝脏来源的损伤相关分子模式(damage associated molecular pattern, DAMP)可被先天免疫系统中的模式识别受体识别并参与免疫应答反应。在受损肝细胞中,线粒体释放的DAMP可引起肝巨噬细胞表面的CD44与其配体透明质酸结合,进而促进与Toll样受体(Toll-like receptor, TLR)4的相互作用,降低T细胞免疫球蛋白黏蛋白3的表达,激活炎症信号通路,诱导巨噬细胞M1极化,产生TNF-α、IL-6、IL-8、IL-1β等炎性因子,进而导致MAFLD的发生[9-11]。

线粒体是产生ROS的主要细胞器,肝细胞中线粒体脂肪酸β氧化能力下降会导致未氧化的脂肪酸在胞质中堆积,转化为甘油三酯(triglyceride, TG)或进入过氧化物酶体进行不完全氧化,导致ROS的过度产生,从而诱发氧化应激和细胞损伤[12]。此外,mtDNA释放到细胞质、细胞外会激活先天免疫信号通路,从而诱导炎症级联反应[13]。mtDNA的先天免疫信号转导诱导NOD样受体热蛋白结构域3(NOD-like receptor family pyrin domain-containing protein 3, NLRP3)炎症小体和环状鸟嘌呤腺嘌呤核苷酸合成酶的活化,激活干扰素基因刺激因子,进而释放促炎因子[14-16]。另外,释放到细胞质中的mtDNA会触发TLR9,激活NF-κB信号通路,释放大量促炎因子,从而导致MAFLD向代谢相关脂肪性肝炎(metabolic dysfunction-associated steatohepatitis, MASH)转化[14]。

1.2 线粒体途径自噬异常 线粒体自噬是一种降解功能失调多余线粒体以维持细胞内稳态的选择性自噬形式,是促进细胞存活的保护性途径[17-18]。研究表明,该途径在调节肝脏稳态中发挥重要作用[19]。线粒体自噬受多条信号通路及相关蛋白的调控,其中最经典的是磷酸酶和张力蛋白同源物诱导的蛋白激酶1(PTEN induced putative kinase 1, PINK1)-E3泛素连接酶(Parkin)通路[20]。在MAFLD早期会出现线粒体受损,此时通过线粒体自噬可有效消除受损的线粒体,而自噬功能缺失与MAFLD的严重程度呈正相关[21]。Parkin作为线粒体自噬信号转导中的关键酶,其缺失会损害线粒体的呼吸

功能，并加剧高脂饮食喂养小鼠的肝脏脂肪积累和胰岛素抵抗的严重程度[22-23]。线粒体受损时，PINK1在线粒体膜上积累并发生磷酸化，进而将Parkin募集到受损的线粒体中，从而启动线粒体自噬[24]。当线粒体自噬减少时，会导致细胞坏死释放DAMP，DAMP激活模式识别受体，触发下游炎症信号通路，从而促进肝脏炎症和MASH的发展[21]。

此外，线粒体自噬还可通过非Parkin依赖性途径诱导。B细胞淋巴瘤/白血病-2相互作用蛋白3（BCL2 interacting protein 3，BNIP3）和FUN14结构域蛋白1是线粒体外膜受体蛋白，在缺氧条件下与自噬体膜上的微管相关蛋白1轻链3（microtubule-associated protein 1 light chain 3，LC3）相互作用，促进线粒体自噬[25]。高松林等[26]基于生物信息学分析的研究及Park等[27]进行的体内外研究均证实，LC3在MAFLD中表达下调。因此，调节肝细胞中线粒体自噬的多种途径，可维持肝脏线粒体功能，对MAFLD的病程进展产生直接影响。

1.3 线粒体途径凋亡异常 凋亡是一种程序性细胞死亡，可由内在或外在信号触发，参与胚胎发育、组织修复及免疫应答等多种生物学效应，对维持机体内环境稳态具有重要作用[28]。当外界刺激损伤肝细胞后，肝脏抗氧化能力下降，产生大量ROS使线粒体能量代谢失衡，触发线粒体凋亡通路[29]。天冬氨酸蛋白水解酶（cysteinyl aspartate specific proteinase，Caspase）是执行细胞凋亡的核心成分，可分为凋亡启动因子和凋亡执行因子。细胞色素C（cytochrome C，CytC）从线粒体被释放到细胞质，募集启动因子Caspase9到凋亡小体继而发生凋亡级联反应，累及下游关键执行因子Caspase3活化，从而导致细胞凋亡。生理状态下，Bcl-2家族的促凋亡蛋白Bax和抗凋亡蛋白Bcl-2共同维持线粒体膜的完整性，共同保护细胞免受细胞凋亡的诱导。MAFLD病理状态下，脂毒性可增强线粒体膜通透性，随之出现线粒体膜电位改变，促使CytC释放至细胞质中，诱发线粒体途径的凋亡异常，从而激活Caspase9/3级联反应，诱导肝细胞凋亡，进而加快MAFLD进程[30]。研究表明，高脂饲料复合四氯化碳诱导的MASH小鼠模型肝组织中凋亡相关基因Caspase3、Caspase8和Bax mRNA的表达显著升高[31]。

1.4 脂质代谢异常 脂质代谢失调是MAFLD病理过程中的重要环节，表现为血浆游离脂肪酸（free fatty acid，FFA）、低密度脂蛋白和TG水平升高。肝脏中脂质蓄积会诱发肝脏脂毒性，进一步导致内质网应激，加速肝细胞衰老与死亡[32]。线粒体甘油3-磷酸脱氢酶（mitochondrial glycerol 3-phosphate dehydrogenase，mGPDH）位于线粒体内膜，是肝脏脂质代谢的关键调节因子，mGPDH缺陷会抑制Ca^{2+}电导通道线粒体通透性转换孔的调节因子线粒体肽基-脯氨酸-反式异构酶亲环蛋白-D的泛素化，从而引起内质网应激，导致肝脏TG积累和脂肪变性；相反，在高脂饮食和遗传诱导的MAFLD模型中，肝脏特异性mGPDH过表达可减轻肝脂肪变性[33]。

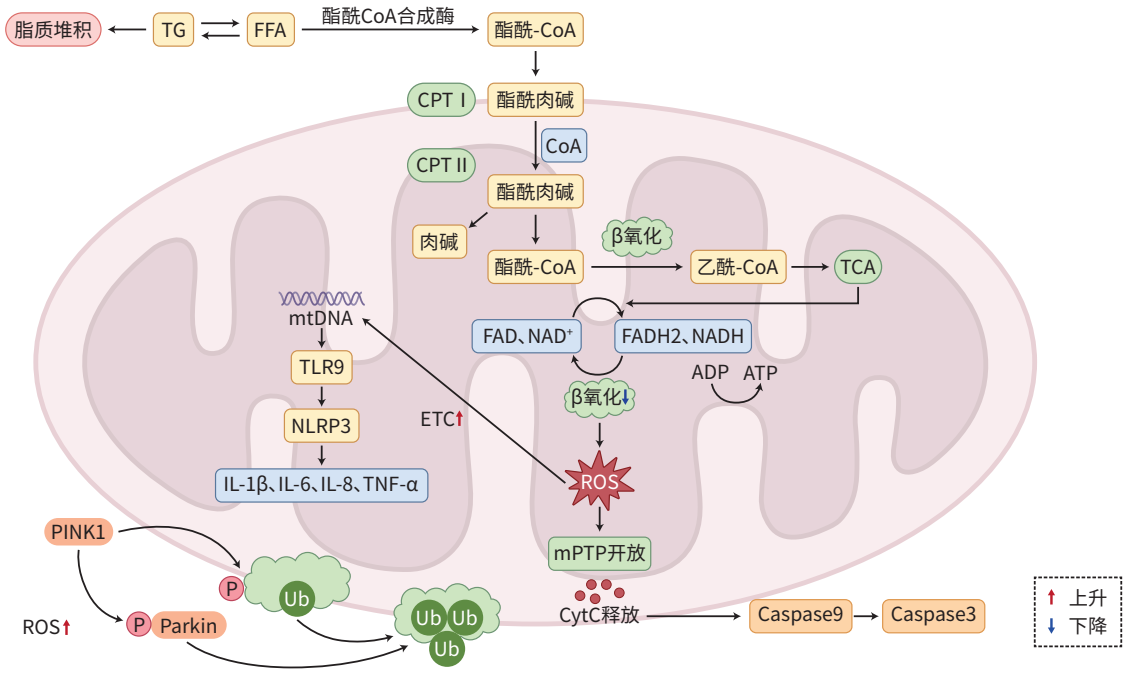
肝脏中FFA的氧化受过氧化物酶体增殖物激活受体γ（peroxisome proliferators activated receptor γ，PPARγ）的调节，该过程主要发生在线粒体，又称脂肪酸β氧化[34]。FFA进入线粒体依赖肉碱棕榈酰转移酶（carnitine palmitoyltransferase，CPT）转运系统，通过线粒体外膜和内膜运输酰基辅酶A。酰基通过线粒体外膜中CPT Ⅰ与肉碱结合形成脂酰肉碱，然后位于线粒体内膜的CPT Ⅱ会将脂酰肉碱重新转化为酰基辅酶A；酰基辅酶A进入三羧酸循环，通过电子传递链生成ATP；长期高脂饮食则会导致丙二酰辅酶A水平升高，抑制CPT Ⅰ，阻碍脂肪酸进入线粒体使脂肪酸β-氧化能力下降，FFA转化为TG，导致肝脂肪变性，从而促进炎症的发生及肝纤维化[35-36]。线粒体功能障碍机制详见图1。

2 中药干预线粒体功能紊乱防治MAFLD的机制

2.1 中药单体成分

2.1.1 多酚 卢万鹏等[37]研究发现，丹酚酸B能上调高脂饮食诱导的ApoE敲除小鼠肝脏中自噬相关蛋白Beclin1、p62、LC3的表达，减轻模型小鼠肝脏炎性损伤及氧化应激，其作用机制可能是通过干预AMP活化蛋白激酶途径调节肝细胞线粒体自噬，从而抑制MAFLD的进展。Li等[38]研究表明，矢车菊素-3-O-葡萄糖苷可减轻MAFLD模型小鼠肝脏氧化应激、NLRP3炎症小体的激活和脂肪变性，同时增加PINK1/Parkin表达和线粒体定位，这可能与矢车菊素-3-O-葡萄糖苷激活PINK1介导的线粒体自噬途径相关。Liu等[39]研究发现，槲皮素能增加小鼠肝组织中LC3 Ⅱ、PINK1、Beclin1的表达，降低p62水平，并可减轻肝脏脂质代谢紊乱，这与槲皮素阻断了高脂饮食对模型小鼠肝脏线粒体自噬的抑制有关。

2.1.2 皂苷 Wang等[40]研究表明，三七的主要活性成分人参皂苷能显著降低脂多糖诱导的线粒体ROS产生，从而减轻线粒体损伤，并通过促进线粒体自噬抑制NLRP3炎症小体激活，抑制炎性因子的分泌，从而延缓MAFLD进程。陈素雯等[41]研究发现，薯蓣皂苷元可显著下调高脂饲料诱导的MAFLD模型大鼠肝组织中雷帕



注：TCA，三羧酸循环；FAD，黄素腺嘌呤二核苷酸；NAD，烟酰胺腺嘌呤二核苷酸；FADH2，还原型黄素腺嘌呤二核苷酸；NADH，还原型烟酰胺腺嘌呤二核苷酸；ADP，二磷酸腺苷；ETC，电子传递链；Ub，泛素；P，磷酸化；mPTP，线粒体通透性转换孔。

图1　线粒体功能障碍机制示意图

Figure 1　Schematic diagram of mitochondrial dysfunction mechanism

霉素靶蛋白、固醇调节元件结合蛋白-1C的表达，上调热休克蛋白60、中链酰基辅酶A脱氢酶、短链酰基辅酶A脱氢酶的表达，这可能与薯蓣皂苷元改善线粒体功能和脂肪酸氧化有关。

2.1.3　*生物碱*　川芎嗪是一种从川芎中提取的生物碱类化合物。Zhou等[42]研究发现，川芎嗪可通过激活PINK1/Parkin介导的线粒体自噬，从而抑制肝细胞坏死性凋亡。小檗碱是从黄连中分离出的一种季铵生物碱，具有抗菌、抗炎和抗癌等作用。Zhu等[43]研究发现，小檗碱可上调MAFLD患者和ob/ob基因小鼠肝脏中介导脂质代谢的关键酶硬脂酰辅酶A去饱和酶1的表达，从而降低肝脏中TG蓄积。Du等[44]研究发现，荷叶碱可以激活转录因子EB介导的自噬-溶酶体途径，从而减轻高脂饮食诱导的MAFLD小鼠肝脂肪变性和胰岛素抵抗，表明荷叶碱可能是治疗MAFLD的潜在药物。

2.1.4　*萜类*　乌药醇是一种从乌药中提取的倍半萜类化合物，具有抗炎、抗氧化的药理作用。刘精武等[45]研究表明，乌药醇提取物可显著上调线粒体自噬调节因子沉默信息调节因子2相关酶（SIRT）1、脂质代谢调节因子PPARα和肥大细胞蛋白酶的表达水平，并下调CD36的表达，表明乌药醇提取物可能通过自噬及脂质代谢途径改善线粒体功能紊乱，从而缓解非酒精性脂肪性肝病模型大鼠肝脏脂质蓄积、氧化应激及炎性损伤。雷公藤内酯是一种环氧二萜内酯化合物，具有抗炎、免疫抑制和抗肿瘤等多重生物活性。研究表明，雷公藤内酯可通过激活AMP活化蛋白激酶调节肝脏线粒体脂质代谢，从而改善高脂饮食诱导的MAFLD[46]。

2.2　*中药复方*　研究表明，大柴胡汤加减方能降低非酒精性脂肪性肝炎患者血脂水平并改善肝功能（研究组总有效率为86.67%，对照组总有效率为64.29%），具有良好的临床疗效与安全性[47]。加味大柴胡汤可通过激活PINK1/Parkin通路增强线粒体自噬，降低小鼠的体质量和血脂水平，减轻氧化应激和炎症损伤，从而改善肝脏受损情况[48]。张梓煊等[49]研究发现，虎金方可显著上调MAFLD模型小鼠肝组织中SIRT1/PGC-1α通路相关蛋白及基因的表达水平，促进线粒体生物合成，从而减少氧化应激与肝脏脂质蓄积，进而缓解MAFLD进展。健肝消脂方可显著改善非酒精性脂肪性肝病模型小鼠肝脏组织病理学变化，降低TC、TG、ALT、AST水平，下调IL-1β、IL-6、TNF-α的表达，上调PINK1、Parkin、Beclin1、LC3蛋白的表达，表明该方可激活PINK1/Parkin通路，诱导线粒体自噬，从而缓解模型小鼠肝脏炎性损伤[50]。既往研究发现，理脾降浊方能显著改善模型小鼠肝重、肝指数及血清TC、TG、低密度脂蛋白-胆固醇、高密度脂蛋

白-胆固醇、ALT和AST水平，上调PPARγ、BNIP3蛋白表达，下调缺氧诱导因子-1α（HIF-1α）蛋白表达，表明该方可能通过调控HIF-1α/PPARγ/BNIP3线粒体自噬途径防治MAFLD[51]。理中汤可显著降低模型大鼠体重、肝湿重、肝指数和血清转氨酶及血脂水平，上调PINK1、Parkin、LC3 Ⅱ表达，提示该方可通过调控线粒体自噬途径改善MAFLD病理改变及肝细胞损伤[52]。肖岩岩等[53]研究发现，健脾清化方可通过调控PGC-1α/PPARα/CPT Ⅰ A通路介导的脂肪酸β氧化，显著改善MAFLD小鼠肝脏炎性损伤，使肝质量和肝指数、血清及肝脏血脂水平明显降低。由此可见，中药复方可通过调节线粒体功能，进一步调控氧化应激、脂质代谢、自噬等，从而达到治疗MAFLD的目的，且在动物及细胞实验中取得了良好效果。

3 小结与展望

中医药主要通过调控氧化应激、自噬、凋亡及脂质代谢等途径，改善线粒体功能障碍，从而发挥治疗MAFLD的作用。深入研究线粒体功能障碍在MAFLD发病过程中的作用机制，将有助于进一步阐明MAFLD各个病理阶段的发病机制，并为MAFLD的治疗提供新的分子靶点。

然而，目前中医药研究仍存在一些不足之处：（1）多数研究集中于动物实验和体外细胞实验，临床研究证据不足，其治疗的可行性与安全性还有待进一步验证；（2）现有研究多集中在各医家的临证自拟方面，尚缺少对经方的研究；（3）中医药具有多活性组分、多靶点、多途径作用的特点，目前对作用机制的研究相对单一。本文通过系统梳理近几年中药单体及复方调控线粒体功能紊乱对MAFLD的干预效应，为进一步应用中医药防治MAFLD提供新了的方向与策略。

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·国外期刊精品文章简介·

Hepatology | 心血管-肾脏-代谢综合征与代谢相关脂肪性肝病肝纤维化进展及肝脏相关事件风险

心血管-肾脏-代谢综合征(CKM)是近年来新提出的整合性代谢性疾病框架。然而，代谢相关脂肪性肝病(MASLD)作为全身代谢的重要表现，尚未得到充分重视。

2025年12月，郑明华和Vincent Wai-Sun Wong作为共同通信作者在*Hepatology*发表的研究，系统评估了CKM分期与MASLD肝纤维化严重程度、进展及肝脏相关事件(LRE)的关系。该研究基于VCTE-Prognosis队列12 097例MASLD患者，结果显示，基线时进展性肝纤维化(LSM ≥10 kPa)的患病率随CKM分期显著递增：CKM 0~1期为9.6%，CKM 2期为18.0%，CKM 3~4期高达31.6%。在中位4.5年的随访中，CKM 2期患者肝纤维化进展风险显著增加，而CKM 3~4期不仅与肝纤维化进展风险显著相关，同时LRE风险也显著升高。

总之，该研究首次在多中心纵向队列中系统证实，处于CKM分期进展阶段(CKM 2期及以上)的MASLD患者，具有显著更高比例的进展性肝纤维化负担；同时，与CKM 0~1期患者相比，其肝纤维化进展及不良肝脏结局的发生风险显著增加。上述发现提示，在CKM分期进展阶段，系统评估和动态监测肝纤维化至关重要。该策略有助于推动MASLD患者心-肝协同管理，并实现早期干预。

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