

# 线粒体复合体I介导的帕金森病运动防治研究进展

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**摘要** 帕金森病(Parkinson's disease, PD)是全球第二大神经退行性疾病,严重影响患者日常生活。线粒体复合体I(mitochondrial complex I, MCI)作为线粒体电子传递链(electron transport chain, ETC)的核心组成部分,其功能障碍与PD的发病机制密切相关。针对MCI功能障碍的治疗方法可能是一种延缓PD进程的有效手段。运动可以有效延缓不同疾病的病程进展,改善日常生活功能及相关行为功能障碍,其机制之一可能是通过上调MCI表达水平介导的。因此,该文旨在综述MCI在PD发生发展和治疗中的作用,重点探讨MCI介导的PD运动防治及其可能机制。

**关键词** 运动; 帕金森病; 线粒体复合体I

## Advance in Mitochondrial Complex I Mediated Movement Prevention and Treatment of Parkinson's Disease

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**Abstract** PD (Parkinson's disease) is the second most common neurodegenerative disease worldwide and seriously affects patients' daily life. MCI (mitochondrial complex I) is a core component of the mitochondrial ETC (electron transport chain), and its dysfunction is closely related to the pathogenesis of PD. Therapies that targeted MCI dysfunction may be an effective strategy to delay the progression of PD. Exercise can effectively delay the progression of different diseases and improve daily life function and related behavioral dysfunction, and one of the mechanisms may be mediated by up-regulating MCI expression levels. Therefore, this article reviews the role of MCI on the pathogenesis and treatment of PD, with a focus on the mechanisms through which exercise may confer protection against PD via MCI.

**Keywords** exercise; Parkinson's disease; mitochondrial complex I

帕金森病(Parkinson's disease, PD)作为发病率仅次于阿尔茨海默病(Alzheimer's disease, AD)的神经系统退行性疾病,其核心病理改变包括中脑黑质致密部(substantia nigra pars compacta, SNpc)多巴胺(dopamine, DA)能神经元渐进性减少以及 $\alpha$ -突触核蛋白( $\alpha$ -synuclein,  $\alpha$ -Syn)病理性沉积,从而引发运动迟缓、震颤、肌强直等一系列严重影响患者日常生活的症状<sup>[1]</sup>。预计到2040年PD的患病人数将增

至1 200万<sup>[2-3]</sup>。线粒体是细胞内极为活跃的动态细胞器,时刻进行着分裂与融合过程,以此维持线粒体的生物发生、功能稳态以及细胞的整体活力<sup>[4]</sup>。线粒体分裂/融合功能障碍与PD的发病紧密相连,而线粒体复合体I(mitochondrial complex I, MCI)功能障碍在PD的发病进程中扮演着重要角色<sup>[5]</sup>。目前,已探索出多种针对MCI功能障碍的方法,以用于PD的治疗<sup>[6-8]</sup>。而运动可以有效延缓不同疾病的病程进展,改善日常生活功能,是经过循证医学验证无创有效、经济易行的康复治疗手段。既往证据表明,运动训练可显著改善PD患者的运动症状和生活质

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量。动物实验研究发现, 跑台运动训练能够修复PD模型小鼠线粒体功能障碍, 从而减少DA能神经元丢失和改善模型小鼠行为功能障碍<sup>[9]</sup>。因此, 该文旨在综述MCI在PD发生发展和治疗中的作用, 重点探讨MCI介导的PD运动防治及其可能机制。

## 1 MCI

线粒体ATP的产生是通过电子传递链(electron transport chain, ETC)中氧化磷酸化(oxidative phosphorylation, OXPHOS)反应进行的。ETC由4种酶复合物(复合物I~复合物IV)和2个移动电子载体辅酶Q(coenzyme Q, CoQ)[疏水性UQ和亲水性细胞色素c(cytochrome c, Cytc)]组成, 位于线粒体内膜(inner mitochondrial membrane, IMM)<sup>[10]</sup>。MCI是ETC的第一个酶复合物, 其被认为是活性氧(reactive oxygen species, ROS)最重要的产出者<sup>[11]</sup>。MCI也是ETC蛋白复合物中最大的(约980 kDa), 由45个蛋白亚基、9个铁硫蛋白(iron-sulfur protein, ISP)(Fe-S)簇和1个黄素单核苷酸(flavin mononucleotide, FMN)分子组成, Fe-S和FMN参与介导NADH至CoQ的电子转移, 其中45个蛋白亚基由44个基因编码: 37个核脱氧核糖核酸(nuclear deoxyribonucleic acid, nDNA)编码和7个线粒体DNA(mitochondrial DNA, mtDNA)编码<sup>[12-13]</sup>。MCI包含7个mtDNA(ND1、ND2、ND3、ND4、ND5、ND6和ND4L)编码和7个nDNA(NDUFV1、NDUFV2、NDUFS1、NDUFS2、NDUFS3、NDUFS7和NDUFS8)编码的核心亚基以及31个辅助亚基, 核心亚基是其酶功能的关键, 而辅助亚基则主要负责维持复合物的组装与结构稳定, 且主要分布于核心亚基周围, 并在膜臂区域富集<sup>[14]</sup>。MCI的7个疏水性亚基(ND1~ND6及ND4L)通过线粒体核糖体完成生物合成, 与此同时, 由nDNA编码的若干核心亚基需经细胞质运输系统转运至线粒体内部。在空间上, mtDNA来源的疏水亚基构成了跨膜区的催化核心模块, 而nDNA编码的7个亚基则在外周区域形成辅助性催化结构, 共同构建出原核MCI的基础框架, MCI外周壁上包含NADH、FMN以及Fe-S等关键功能元件, 其中FMN作为主要电子传递载体, 通过与Fe-S的特异性结合, 建立起FMN与末端电子受体泛醌之间的电子传递通路<sup>[15]</sup>。越来越多的研究证明, MCI在线粒体呼吸链中起着重要作用, 是OXPHOS-ETC的切入

点, 其中2个电子经FMN介导, 通过Fe-S簇接力传递至泛醌, 同时驱动4个质子从线粒体基质经跨膜结构域泵入膜间隙, 随后电子通过复合物III与复合物IV的级联传递, 协同实现10个质子的定向跨膜转运, 最终在内膜两侧建立电化学质子梯度。该梯度所储存的自由能通过复合物V的旋转催化机制, 驱动ATP的生物合成<sup>[16]</sup>。总之, MCI一旦受损就会影响基本的细胞过程(如代谢、氧化还原平衡、Ca<sup>2+</sup>调节、细胞凋亡和信号转导), 最终可能导致细胞死亡<sup>[17-18]</sup>。

## 2 MCI与PD

研究表明, 散发性和遗传性PD均存在MCI缺陷<sup>[19]</sup>。BUNEEVA等<sup>[20]</sup>研究发现, PD患者SNpc中的MCI发生氧化损伤, 提示ROS可影响MCI。而KALOGEROPULOU等<sup>[21]</sup>和CHEN等<sup>[22]</sup>研究显示, 与健康对照组相比, PD患者成纤维细胞MCI活性显著降低, ATP产生减少。此外, 还有研究观察到与7例对照组相比, 17例PD患者多个脑区的MCI免疫组织化学染色均减少<sup>[23]</sup>。另外, 多项研究发现, 在PD个体的DA能神经元SNpc线粒体中出现DNA维持受损和MCI缺陷<sup>[24-26]</sup>。对于MCI在PD模型动物中的变化也有相关研究报道。研究表明, 鱼藤酮诱导的PD模型小鼠MCI活性降低、线粒体完整性受损, 从而造成黑质DA能神经元变性丢失, 模型小鼠出现行动迟缓等PD相关行为功能障碍<sup>[27]</sup>。MPTP作为一种神经毒素也常用于PD模型的建立。研究表明, MPTP在脑组织内经生物转化生成活性代谢产物MPP<sup>+</sup>, 其机制涉及DA转运体介导的跨膜运输, 促使该毒素特异性富集于DA能神经元内, 进而抑制MCI的电子传递功能, 引发线粒体基质内ROS的爆发性生成, 最终抑制线粒体呼吸, 致使细胞能量稳态失衡<sup>[28]</sup>。虽然这些MCI缺陷或活性下降的原因尚不清楚, 但有研究推测它们有助于神经退行性过程, 可引起DA能神经元变性。有研究显示, MCI功能障碍可引发PD多重病理效应: (1) NADH积累导致NAD<sup>+</sup>/NADH值下降及氧化还原失衡<sup>[29]</sup>; (2) 氧化磷酸化抑制、ATP耗竭与能量不足<sup>[30]</sup>; (3) 质子转移受损致使线粒体膜电位(mitochondrial membrane potential, MMP)降低, Cytc释放并诱导神经细胞凋亡<sup>[31]</sup>, 此外, MCI功能障碍还通过增加ROS生成和胞内钙离子水平, 激活神经炎症、 $\alpha$ -Syn聚集及线粒体功能障碍等致病机制,

形成恶性循环,最终加速PD进展<sup>[32]</sup>。综上,MCI是PD多种致病机制的关键枢纽,MCI功能障碍可能会导致黑质DA能神经元能量代谢障碍、ROS积累以及氧化应激,进而引发神经元变性死亡。因此,改善MCI功能障碍在延缓PD(患者和模型动物)进程中起着关键作用。一项临床试验研究发现,接受褪黑素治疗的PD患者MCI活性和呼吸控制率显著增加,血浆样本中脂质过氧化物、一氧化氮代谢物和羰基显著减少<sup>[33]</sup>。另外,一种天然的多酚类化合物白藜芦醇能够提高PD患者线粒体活性(MCI和柠檬酸合成酶活性提高、基础耗氧量和线粒体ATP产生增加以及乳酸含量的降低),其机制可能是通过激活受体- $\gamma$ 共激活因子-1 $\alpha$ (peroxisome proliferator-activated receptor  $\gamma$  coactivator 1-alpha, PGC-1 $\alpha$ )<sup>[34]</sup>。此外,在鱼藤酮诱导的PD模型大鼠中,非索酮(Fisetin)治疗通过靶向鱼藤酮对MCI活性的抑制显著改善了模型大鼠在圆桶试验中的运动功能障碍,抑制了氧化应激以及修复相关线粒体功能障碍<sup>[35]</sup>。综上,药物治疗通过调节MCI活性改善MCI功能,从而改善线粒体能量代谢和减少氧化损伤,为PD药物防治提供了新的思路。

### 3 运动与PD

运动是一种辅助和替代的非药物治疗策略,各种类型的运动疗法在改善PD相关行为功能障碍方面的积极作用越来越受到关注。有氧运动是PD管理的普遍处方,它可缓解PD患者运动症状和增强PD患者认知功能。美国物理治疗协会(American Physical Therapy Association, APTA)在其PD临床实践指南中鼓励物理治疗师对PD患者实施中等强度至高强度的有氧运动(60%~85% HRmax),以改善耗氧量和行为功能障碍<sup>[36]</sup>。研究发现,无论使用哪种中等强度至高强度有氧运动模式,在研究中均观察到相似的结果:均可不同程度提升PD患者的步行能力、平衡功能及肌力,并在一定程度上改善疲劳、焦虑等非运动症状,其中有氧运动形式包括跑步机训练<sup>[37]</sup>、户外自行车<sup>[38]</sup>、快走<sup>[39]</sup>、水上运动<sup>[40]</sup>、北欧步行<sup>[41]</sup>等。此外,在相似强度水平下进行的其他形式的有氧运动,如划船、爬楼梯、舞蹈等具有类似的治疗效果<sup>[42]</sup>。抗阻训练也是PD运动干预的基本组成部分,旨在改善肌肉力量、耐力和运动能力。通过针对受PD相关僵硬和

无力影响的特定肌肉群,抗阻训练有助于缓解PD患者运动症状和提高其整体体能,如举重、抗阻带练习和基于健身器械锻炼的硬拉和卧推等抗阻训练方式可以适应PD患者的需求<sup>[43-44]</sup>。平衡训练是PD患者物理治疗的关键组成部分,旨在改善姿势控制、步行能力,并预防患者跌倒。针对PD患者(Hoehn & Yahr分期1.5~3)平衡的康复治疗不仅可以使其平衡能力和运动能力显著改善,还可使皮质运动抑制能力明显增强<sup>[45]</sup>。近年来,关于身心锻炼对PD患者相关行为功能障碍影响的也研究越来越多。研究表明,瑜伽练习可使轻度至中度(Hoehn & Yahr分期1~3)PD患者运动功能、姿势稳定性、平衡控制能力、功能性步态和冻结步态显著改善,本体感知敏锐度显著提高<sup>[46]</sup>。研究发现,长期太极拳训练干预可显著改善PD患者的运动功能、步态、平衡和功能灵活性,且各指标改善较瑜伽和平衡训练更有效<sup>[47]</sup>。此外,普拉提、舞蹈和探戈也被用于PD患者的康复治疗,并被证实在改善PD患者静/动态平衡能力、功能灵活性和下肢力量等方面显示出积极的效益,被认为是改善PD患者功能表现的有效策略之一<sup>[48]</sup>。

综上,多种运动疗法在PD全程管理中均具有潜在益处。然而,目前尚缺乏高质量的随机对照试验(randomized controlled trial, RCT)明确哪种运动类型对改善患者功能表现最有效,未来需通过扩大样本量进一步比较不同运动的优势。

### 4 运动与MCI

研究表明,有氧运动可调节正常啮齿类动物MCI活性或表达。GUSDON等<sup>[49]</sup>研究发现,17天的跑步机训练(5次/周,19 m/min,60 min/次)可使老年小鼠皮层和纹状体中MCI活性显著提高,呼吸速率显著增加。BAYOD等<sup>[50]</sup>研究表明,长期自愿跑轮运动(3天/周,持续25周)可使衰老模型小鼠海马区MCI活性显著增加,ROS生成减少。MARQUES-ALEIXO等<sup>[51]</sup>研究发现,跑台运动和自愿跑轮运动(60 min/天,5天/周,持续12周)可使大鼠大脑皮层和小脑MCI亚基水平增加,氧化应激水平显著降低。另外,LUO等<sup>[52]</sup>研究显示,长期的游泳训练(5次/周,30 min/天,持续10周)可使老年大鼠海马区MCI活性显著提高,与年龄有关的认知功能障碍显著改善。此外,在病理状态下,运动也能通过调节MCI



活性改善小鼠学习认知能力。BO等<sup>[53]</sup>研究发现, 长期的跑台训练(5次/周, 11 m/min, 30 min/次, 共20周)可使阿尔茨海默病模型小鼠海马区MCI活性显著提高, ROS生成减少以及mtDNA氧化损伤减轻, 模型小鼠的学习能力和记忆能力显著改善, 如在Y迷宫试验中表现出自发交替行为显著增加, 被动回避实验中的保留潜伏时间显著延长。

总之, 不同参数(强度、频率、持续时间)的运动训练通过调节MCI活性改善脑功能并缓解神经疾病进展。然而, 各类运动模式对不同疾病状态下MCI的作用机制亟待深入研究。

## 5 MCI介导的PD运动防治

在PD中, 有证据表明MCI活性下降会促进Cyt c的释放, 使ATP的产生减少、ROS的产生大量增加以及细胞内钙离子超载, 最终导致氧化应激的发生<sup>[54]</sup>。氧化应激增加会导致线粒体功能障碍, 从而导致ROS和mtDNA缺失突变增加, 线粒体ROS激活 $\alpha$ -Syn, 而 $\alpha$ -Syn的异常聚集所产生的毒性作用进一步形成莱维小体病, 这些聚集体还可能导致内质网功能障碍、突触功能障碍以及MCI的功能受到抑制, 莱维小体病通过上调TNF- $\alpha$ 、IL-1或IL-6等炎症因子的表达来激活小胶质细胞, 从而导致神经炎症发生并促进细胞凋亡, 此外, Parkin蛋白的上游因子通过PINK1/Parkin通路调控线粒体自噬, 维持线粒体稳态, PINK1基因缺失会破坏线粒体的降解、形态和运输, 导致线粒体功能障碍, 进而加速神经元死亡, 从而促进PD病情的发展, 最终引发PD相关行为功能障碍<sup>[55]</sup>。而CHUANG等<sup>[56]</sup>研究发现, 4周的跑步机训练(30 min/天, 7天/周, 15 m/min)可使6-OHDA构建的PD模型大鼠纹状体MCI表达水平显著上调, 恢复了线粒体功能, 降低了氧化应激水平, 并使DA能神经元活力得到了显著改善, 模型大鼠步态参数(最大面积、摆动速度、步长和站立相方面)也得到了显著改善, 甲基苯丙胺引起的旋转现象显著减少。FERREIRA等<sup>[57]</sup>研究表明, 为期1周的跑步机训练(40 min/天, 3天/周, 10 m/min)均可使6-OHDA构建的PD模型大鼠纹状体MCI表达水平显著上调, 而模型大鼠在步态测试中只有步幅数据显示运动1周后有所改善; 而运动4周后所有步态参数显著改善以及阿扑吗啡旋转实验中模型大鼠的旋转圈数显著减少。

综上, 运动可能通过上调MCI表达水平, 致使ROS产生减少, 降低 $\alpha$ -Syn异常聚集的毒性作用, 调节TNF- $\alpha$ 、IL-1或IL-6等炎症因子的表达, 最终通过抗氧化应激、抗炎、修复线粒体功能障碍等功能介导PD行为功能障碍的改善(图1)。但这仍需要做进一步的研究证实。

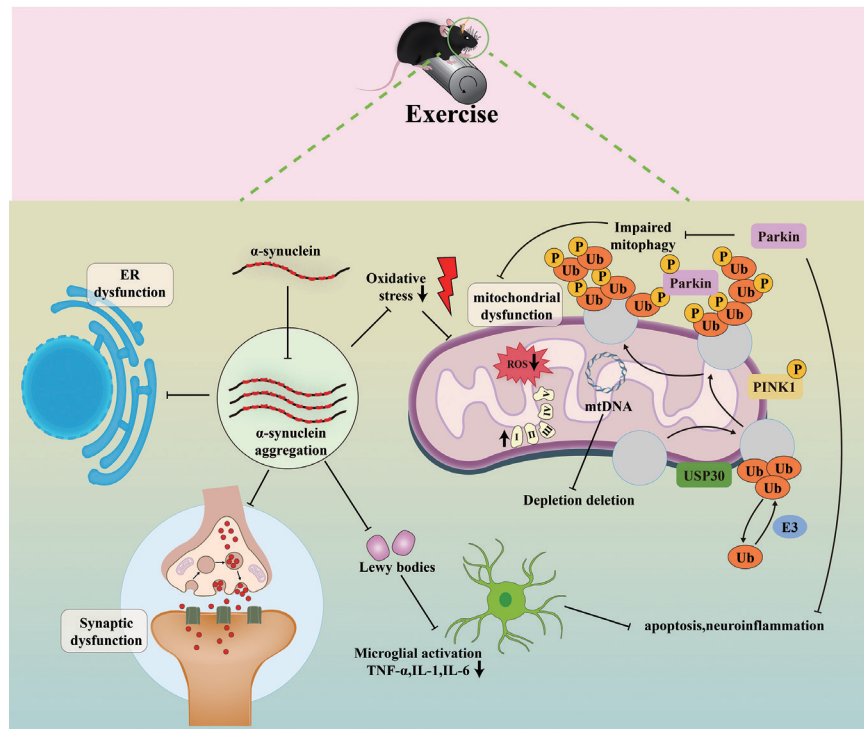
## 6 小结与展望

MCI在PD神经炎症、线粒体功能障碍、氧化应激等机制中可能起重要作用, 因此, 对MCI的深入研究将为PD的治疗提供新的理论依据和潜在治疗靶点。运动作为PD的一种非药物干预手段, 可显著改善PD患者相关行为功能障碍, 可能是通过上调MCI表达水平从而抑制神经炎症、氧化应激以及修复线粒体功能障碍等实现的。而这仍需要做进一步的研究证实。

不同方式、强度、持续时间的运动训练对PD中MCI的影响是怎么样的呢? 各类运动模式对PD状态下MCI的作用机制又是怎么样的呢? 未来就这些问题还需要做进一步的探索和研究。因此, 探索MCI在PD运动防治中的作用可能是未来防治PD新的关注点。

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↓: 下调; ↑: 上调; ⊥: 抑制; →: 促进。

↓: downregulation; ↑: upregulation; ⊥: inhibition; →: facilitation.

图1 MCI介导的PD运动防治(根据参考文献[55]修改)

Fig.1 MCI mediated exercise prevention and treatment in PD (modified from reference [55])

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