·综 述·

运动康复训练调节线粒体损伤对慢性阻塞性肺疾病骨骼肌功能障碍的影响

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摘要 慢性阻塞性肺疾病(COPD)是一种异质性的慢性呼吸系统疾病,骨骼肌功能障碍作为COPD常见的并发症之一,主要临床表现为肌力和肌耐力下降、肌纤维类型改变、骨骼肌质量降低。线粒体损伤是引起骨骼肌功能障碍的关键因素之一。线粒体不仅为骨骼肌提供能量,同时也参与活性氧(ROS)产生、自噬和蛋白质周转,对维持骨骼肌正常功能具有重要意义。本研究阐述COPD骨骼肌功能障碍的线粒体改变、COPD骨骼肌功能障碍的线粒体损伤作用机制以及运动康复训练对COPD骨骼肌线粒体损伤的潜在影响,旨在进一步明确线粒体和骨骼肌功能间的关系,为优化COPD骨骼肌功能障碍的运动康复方案提供参考。其中,COPD骨骼肌功能障碍的线粒体改变主要包括线粒体呼吸链受损、线粒体自噬激增和线粒体生物发生减少3个方面;COPD骨骼肌功能障碍的线粒体损伤作用机制主要包括增加骨骼肌降解、减少骨骼肌生成和干扰骨骼肌分化;运动康复训练对COPD骨骼肌线粒体损伤的潜在影响主要包括运动康复训练可修复COPD患者骨骼肌线粒体呼吸链、调控COPD患者骨骼肌线粒体自噬和促进COPD骨骼肌线粒体生物发生。下一步研究仍需探讨线粒体对维持骨骼肌正常功能结构的关键作用、COPD骨骼肌功能障碍的发生原理以及运动康复训练调节线粒体损伤改善COPD骨骼肌功能障碍的具体作用机制,以期为运动康复训练干预COPD骨骼肌功能障碍提供参考依据。

关键词 慢性阻塞性肺疾病;骨骼肌功能障碍;线粒体损伤;线粒体自噬;运动康复训练

慢性阻塞性肺疾病(chronic obstructive pulmonary disease,COPD)是一种异质性的慢性呼吸系统疾病,其肺部主要表现为气道、肺实质和肺血管系统的损伤和重塑[1]。除肺部症状外,骨骼肌功能障碍是COPD常见的并发症之一,由缺氧、炎症、氧化应激、营养不良、废用、蛋白合成和分解不平衡、类固醇激素的使用和线粒体损伤等多种因素引起[2]。这些因素共同作用造成骨骼肌功能、代谢和解剖结构改变。COPD患者骨骼肌功能障碍的主要临床表现为肌力和肌耐力下降,患者肌纤维类型改变和骨骼肌质量降低,致使肌肉做功减少,导致活动能力减退[3-4]。骨骼肌功能障碍最终导致生活质量和运动能力下降,加速疾病恶化。

线粒体损伤是引起骨骼肌功能障碍的关键因素之一[5]。线粒体不仅为骨骼肌提供能量,同时也参与活性氧(reactive oxygen species,ROS)产生、自

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噬和蛋白质周转,对维持骨骼肌正常功能具有重要意义[6]。有研究表明,COPD患者骨骼肌线粒体损伤主要表现为密度降低、生物合成减少、呼吸链复合体活性和偶联受损、活性氧产生增加等,并可能导致细胞凋亡[7]。线粒体损伤影响骨骼肌正常结构、代谢和功能,造成骨骼肌萎缩和耐力下降[8]。但线粒体损伤如何引起骨骼肌功能障碍,以及以线粒体为靶点修复受损骨骼肌的内在作用机制目前尚无明确定论。本研究阐述COPD骨骼肌功能障碍的线粒体改变、COPD患者骨骼肌功能障碍的线粒体损伤作用机制以及运动康复训练对COPD骨骼肌线粒体损伤的潜在影响,旨在进一步明确线粒体和骨骼肌功能间的关系,为优化COPD骨骼肌功能障碍的运动康复方案提供参考。

1 COPD骨骼肌功能障碍的线粒体改变

线粒体是造成COPD骨骼肌功能障碍的细胞器之一,参与骨骼肌功能、代谢和结构的改变。线粒体的正常运作依赖于内稳态,需要线粒体自噬、线粒体生物发生和活性氧产生等过程共同协调,上述环节发生紊乱将直接导致线粒体功能障碍。COPD患者骨骼肌线粒体呼吸链受损、线粒体自噬激增和生物发生减少,无法有效地发挥能量代谢和信息传递作用,这些变化会影响骨骼肌正常功能。

1.1 线粒体呼吸链受损

线粒体呼吸链在机体正常功能的运行过程中发挥关键作用,其损伤与生理功能紊乱具有密切联系,即使是最低程度的改变也会导致疾病发生[9]。线粒体呼吸链由位于内膜上的5个复合体组成,利用电子传递过程,通过氧化磷酸化产生腺嘌呤核苷三磷酸(adenosine-triphosphate,ATP),同时电子传输产生ROS[10]。有研究显示,COPD患者骨骼肌线粒体复合体Ⅰ、Ⅱ、Ⅳ减少,表明患者骨骼肌线粒体呼吸链受损[11-12]。COPD全球倡议(global initiative for chronic obstructive lung disease,GOLD)显示,3/4级COPD患者骨骼肌内的线粒体复合体Ⅰ表达明显降低,但在2级患者的骨骼肌中未检测出[13]。

线粒体呼吸链受损将影响电子传递,导致机体能量发生过程和呼吸链底物ROS产生失衡。一方面,COPD患者ATP生成不足,骨骼肌中ATP最大产量减少,能量供给不足导致运动耐力降低[14]。另一方面,从COPD患者骨骼肌中分离出的高浓度ROS相关产物引发氧化应激,造成线粒体功能障碍,继而破坏骨骼肌细胞成分[15]。有研究表明,线粒体损伤在中度至重度(GOLD 2~4级)COPD患者骨骼肌中发生,且伴随明显的氧化应激,提示线粒体损伤可能在COPD患者中、晚期持续存在,与骨骼肌功能障碍出现时期吻合,并产生大量的ROS而加重疾病进程[11-13]。以上研究表明,COPD患者骨骼肌线粒体呼吸链受损,可能会引起内稳态失衡和能量供给不足,造成骨骼肌正常生理活动紊乱。

1.2 线粒体自噬激增

线粒体自噬是重要的线粒体质量调控系统,能够选择性地清除受损线粒体,以维持线粒体质量和避免损伤线粒体累积[16]。线粒体自噬可以保护骨骼肌免受线粒体ROS和线粒体DNA(mitochondrial DNA,mtDNA)失调导致的损伤(如引起炎症和细胞凋亡等)。因此,适当清除受损线粒体是至关重要的[17]。线粒体自噬主要有泛素依赖性和受体介导2种自噬途径,均在COPD患者骨骼肌中过度激活。GUO等[18]发现COPD患者骨骼肌泛素依赖性和受体介导的线粒体自噬相关基因表达增加,受体介导的线粒体自噬相关蛋白比例升高,提示线粒体自噬可能亢进。LEERMAKERS等[19]发现COPD患者骨骼肌中泛素依赖性线粒体自噬相关的E3泛素连接酶Parkin基因和蛋白质表达水平较高,并与FEV_1%预测值呈负相关关系,在疾病严重程度更高的COPD骨骼肌中表达更为明显。此外,也有研究表明COPD患者泛素依赖性自噬信号减少,导致线粒体ROS增加并激活肌管萎缩相关通路,造成骨骼肌质量减少[20]。因此,COPD患者骨骼肌中线粒体自噬水平发生改变,这种改变与肺功能和骨骼肌损害相关,虽然大部分研究发现线粒体自噬水平升高,但线粒体自噬水平在COPD骨骼肌中的确切变化情况尚未形成统一定论。

1.3 线粒体生物发生减少

线粒体生物发生是线粒体质量增加的过程,能够增加线粒体体积和数量,但这一过程在COPD患者骨骼肌中常常受到抑制。REMELS等[21]认为COPD患者股外侧肌线粒体生物发生相关因子的基因表达明显减少,会直接降低线粒体生物发生的驱动力,导致COPD患者骨骼肌中线粒体含量下降[22]。有研究显示,COPD患者股外侧肌线粒体密度标志性蛋白柠檬酸合酶活性明显降低,提示线粒体密度下降[23],线粒体密度和活性不足可能会导致COPD患者骨骼肌功能障碍以及运动能力下降[24]。ZHANG等[25]研究发现,COPD患者线粒体密度降低将直接影响患者的体质量与肌肉含量,低肌肉量COPD患者线粒体生物发生不足更为严重。线粒体生物发

生减少还会影响骨骼肌氧化能力，骨骼肌更易受到氧化耗竭的影响，导致抗疲劳能力下降[23]。因此，COPD患者骨骼肌功能障碍可能与骨骼肌线粒体生物发生减少，线粒体体积和数量降低，线粒体正常功能受影响有关。

2 COPD患者骨骼肌功能障碍的线粒体损伤作用机制

骨骼肌功能维持与线粒体运行密切相关，线粒体参与骨骼肌蛋白质周转、能量供给和信号传递等过程。线粒体损伤可能会导致骨骼肌功能障碍，其作用机制可能与增加骨骼肌降解、减少骨骼肌生成和干扰骨骼肌分化3个方面有关。

2.1 增加骨骼肌降解

骨骼肌功能与肌肉质量呈正相关关系，质量减少将造成肌力降低[26]。有研究发现，COPD患者分解代谢增强，骨骼肌蛋白降解加快，导致骨骼肌肌纤维数量减少[27]。线粒体是蛋白质质量控制的核心细胞器，线粒体损伤将导致蛋白质稳态破坏，增加骨骼肌降解。线粒体自噬能够影响COPD骨骼肌蛋白质调控。线粒体自噬的程度与肺功能损伤和骨骼肌萎缩严重程度相关[18]。当线粒体自噬发生时，PTEN诱导的假定蛋白激酶1（PTEN-induced kinase 1，PINK1）固定到外膜并招募Parkin，Parkin募集导致线粒体融合蛋白2降解，启动受损线粒体和微管相关蛋白质轻链3（light chain 3，LC3）的定位并形成自噬体将其分解，避免堆积[17]。在COPD患者中，线粒体自噬增加导致PINK1、Parkin和LC3水平同步升高，但整体却表现出易位到线粒体关键蛋白Parkin减少，提示COPD骨骼肌中线粒体自噬异常[20,28]。这种自噬异常导致PINK1在线粒体外膜稳定之后，无法招募并激活足量Parkin；Parkin不足会减少活化的E3泛素连接酶数量，影响外膜蛋白的泛素化以及自噬体蛋白在线粒体外膜的累积，最终导致自噬体无法与溶酶体形成自噬溶酶体，阻碍蛋白酶体的识别，引起受损线粒体的堆积[20,29]。若线粒体自噬异常，无法及时清除受损线粒体，将进一步影响骨骼肌分解代谢过程并加快骨骼肌质量下降。有研究显示，Parkin不足会改变线粒体自噬水平，降低线粒体呼吸链复合体Ⅰ和Ⅱ活性，激活肌肉特异性环指蛋白1（muscle RING-finger protein-1，MuRF-1）介导的肌球蛋白重链（myosin heavy chain，MHC）降解，引起骨骼肌萎缩[30]。

线粒体作为生物氧化发生的主要场所之一，由线粒体损伤导致的氧化系统和抗氧化系统失衡将造成氧化应激，诱导线粒体通透性转变与mtDNA失调，引起肌肉永久性损伤[31-32]。受损细胞释放的mtDNA被认为是损伤相关分子模式，影响线粒体呼吸链加速ROS产生，诱导COPD患者骨骼肌萎缩[33]。一方面，ROS通过激活对其敏感的核因子-κB（nuclear factor-κB，NF-κB）转录因子和叉头转录因子O（forkhead box O，FoxO）上调肌肉萎缩盒F（muscle atrophy F-box protein，MAFbx/Atrogin1）和MuRF-1，并通过泛素26 s蛋白酶体通路加快COPD患者骨骼肌降解[34-37]。COPD患者骨骼肌活体组织检查结果也显示磷酸激酶B（protein kinase B，PKB/Akt）/FoxO通路和凋亡信号上调，导致肌萎缩相关因子增多，促进骨骼肌萎缩[38-40]。另一方面，ROS还促进线粒体通透性转变，释放细胞色素C（cyto chrome C，Cyt C）激活c-Jun氨基末端激酶/B淋巴细胞瘤相关蛋白2相关蛋白X/半胱氨酸天科氨酸蛋白酶（Caspase-3）通路诱导细胞凋亡，降低骨骼肌质量，而COPD患者骨骼肌中发现Cyt C增加，导致骨骼肌降解加快[41-43]。

受损细胞释放的mtDNA和ROS诱导炎症反应，造成COPD患者骨骼肌萎缩，引起肌力下降[44-46]。有研究表明，炎症因子肿瘤坏死因子α（tumor necrosis factor-α，TNF-α）与肌力呈负相关关系，在COPD患者骨骼肌中表达增加导致肌力下降[47-48]。TNF-α可以减少IκB激酶α激活经典的NF-κB通路，从而上调MuRF1的表达激活泛素-蛋白酶途径加速肌肉分解[49-50]。TNF-α还可以激活p38-促分裂素原活化蛋白激酶途径，通过Foxo4刺激Atrogin1基因表达促进骨骼肌萎缩[51-52]。COPD患者骨骼肌线粒体自噬增加，ROS诱导氧化应激与mtDNA失调引发炎症反应共同作用，导致骨骼肌蛋白质分解加快，最终引起骨骼肌萎缩。

2.2 减少骨骼肌生成

COPD患者骨骼肌线粒体密度减少、线粒体生物发生能力降低还会使肌肉生成减少，导致骨骼肌功能障碍[53]。过氧化物酶体增殖物激活受体γ共刺激因子（peroxisome proliferators-activated receptor γ coactivator-1 alpha，PGC-1α）是线粒体生物发生的主要调节剂，也是骨骼肌代谢稳态的核心激活剂，以PGC-1α为枢纽的信号调节系统能减少细胞凋亡，促进蛋白质合成和细胞增殖[54]。BRAULT等[55]研究显示，PGC-1α特异性表达可以抑制Foxo3通路诱导Atrogin-1和MuRF-1表达，提示PGC-1α可以通过抑制骨骼肌萎缩相关基因表达，增加骨骼肌质量。在运动肌中，PGC-1α特异性诱导胰岛素样生

长因子-1(insulin-like growth factor-1,IGF-1)并抑制肌肉生长抑制素表达,促进骨骼肌肥大[56]。IGF-1是肌肉代谢的主要途径,能够通过磷脂酰肌醇3-激酶(phosphoinositide 3-kinase,PI3K)/Akt/哺乳动物雷帕霉素靶蛋白(mammalian target of rapamycin,mTOR)途径增加骨骼肌蛋白质合成,抑制ROS产生以抵抗氧化损伤[57]。此外,激活mTOR/PGC-1α轴可以增加线粒体生物发生,提高线粒体质量并上调氧化磷酸化水平,促进ATP合成,以维持骨骼肌正常运转[58]。mTOR也是重要的骨骼肌生长因子,缺失或减少会造成肌纤维直径减小以及严重肌病发生[59]。上述研究均表明线粒体生物发生因子PGC-1α及其相关信号通路是保证线粒体功能、避免发生骨骼肌功能障碍的重要途径。

COPD患者骨骼肌中PGC-1α表达降低,不仅会减少骨骼肌生成,还会促进细胞凋亡,从而加快骨骼肌萎缩。研究发现,COPD患者骨骼肌中受PGC-1α特异性诱导的IGF-1水平降低,导致PI3K/Akt磷酸化抑制,造成mTOR/PGC-1α失活,最终影响骨骼肌合成代谢[60]。在久坐的COPD患者骨骼肌中也发现IGF-1表达下降,致使Akt磷酸化抑制并减少PGC-1α表达,PGC-1α的降低导致Foxo3a与细胞核DNA的结合增强,进一步提高促凋亡因子Bim蛋白水平,加快骨骼肌细胞凋亡,从而影响骨骼肌再生[61-62]。生肌因子减少,而凋亡因子增加,会导致骨骼肌生成降低。PGC-1α下调还将打破氧化与抗氧化平衡,间接影响骨骼肌生成。PGC-1α能够激活调控抗氧化的关键因子细胞核呼吸因子1/2(nuclear respiratory factor 1/2,Nrf1/2)诱导线粒体生物发生,而COPD患者出现明显的Nrf2失活,导致线粒体生物发生减少和抗氧化防御下降,造成骨骼肌功能障碍[63]。PGC-1α及其相关通路失活将加剧COPD患者骨骼肌氧化应激并抑制骨骼肌生成,诱发骨骼肌萎缩。

除了参与IGF-1/Akt/mTOR途径外,PGC-1α也是腺苷酸激活蛋白激酶[adenosine 5′-monophosphate (AMP)-activated protein kinase,AMPK]的下游因子,AMPK表达减少将抑制PGC-1α活性,进而降低线粒体生物发生,影响骨骼肌质量。AMPK/PGC-1α通路能够改变异常的线粒体自噬,增加线粒体生物发生,减少过度的细胞凋亡,从而改善骨骼肌纤维超微结构,抑制骨骼肌质量下降[64]。此外,AMPK能够上调解偶联蛋白表达,限制ROS产生,提高线粒体功能和含量,从而影响骨骼肌结构和功能[65]。研究发现,COPD患者骨骼肌中AMPK/PGC-1α失活,导致ROS水平和线粒体功能改变,间接影响骨骼肌质量[39,50]。

mtDNA和ROS失调诱导炎症反应发生,炎症因子通过降低PGC-1α表达,限制线粒体生物发生,从而减少骨骼肌质量。研究发现,COPD患者骨骼肌中TNF-α mRNA和蛋白水平增加,TNF-α能够通过抑制IGF-1/Akt/mTOR通路,间接降低PGC-1α表达水平,导致蛋白质合成减少并干扰线粒体生物发生影响肌肉质量[7,26,66]。TNF-α也可以直接抑制PGC-1α促进NF-κB通路活化,减少成肌分化抗原(myogenic differentiation antigen,MyoD)mRNA表达,影响肌肉再生,加速骨骼肌萎缩[57,67]。MyoD能够增加成肌细胞数量,NF-κB可以抑制MyoD mRNA和蛋白表达,影响骨骼肌细胞生长[67-68]。COPD患者股外侧肌和香烟诱导的COPD小鼠腓肠肌中也发现NF-κB通路激活伴随MyoD表达降低,提示骨骼肌细胞数量减少[69]。

综上所述,PGC-1α作为线粒体生物发生的中心因子,与多个途径共同作用,促进骨骼肌生成,但COPD患者骨骼肌中PGC-1α表达水平降低导致线粒体功能障碍和蛋白质合成减少,最终影响骨骼肌质量和功能。

2.3 干扰骨骼肌分化

骨骼肌分化开始时,成肌细胞需要与预先存在的肌管融合,而肌管系统代谢活跃,高度依赖线粒体氧化磷酸化产生ATP以满足能量需求[70]。在骨骼肌分化过程中,需要线粒体活性增加才能保持正常生理功能。有研究发现,线粒体自噬是成肌细胞分化的关键环节,敲除PINK1以抑制线粒体自噬将导致分化的小鼠成肌细胞(C2C12细胞)中肌细胞生成素mRNA水平下降,进而造成骨骼肌分化受损[70-71]。此外,线粒体自噬能够减少ROS产生,提高抗氧化酶活性,减少成肌细胞分化过程中的氧化应激和凋亡信号传导,保证细胞氧化还原稳态[72]。COPD患者骨骼肌线粒体自噬水平虽有所升高,但仍不足以清除受损线粒体,这将影响骨骼肌分化。

PGC-1α作为线粒体生物发生的关键因子,除了影响线粒体质量外,还可以驱动Ⅱ型肌纤维转化为Ⅰ型肌纤维,从而提高骨骼肌抗疲劳能力[73]。COPD患者骨骼肌AMPK/SIRT1/PGC-1α通路失活,降低PGC-1α蛋白水平导致Ⅰ型肌纤维减少,影响骨骼肌耐力和抗疲劳性[39,67,74]。除PGC-1α外,上游因子AMPK和SIRT1也能促进肌纤维类型的转换。

有研究发现，抑制AMPK表达会降低主要组织相容性复合体（major histocompatibility complex，MHC）蛋白水平，而AMPK失活还会影响烟酰胺腺嘌呤二核苷酸减少SIRT1表达[75]。SIRT1能够促进Ⅱ型肌纤维向Ⅰ型肌纤维转变，而下游因子PGC-1α与肌细胞增强因子2蛋白共同激活转录并作为钙调神经磷酸酶信号传导的靶点，也和Ⅰ型肌纤维基因表达有关[76]。AMPK/SIRT1/PGC-1α通路的3个关键因子都能促进肌纤维类型转化以保证骨骼肌Ⅰ型肌纤维比例，但COPD患者骨骼肌中线粒体生物发生相关的PGC-1α及其上游因子失活影响Ⅰ型肌纤维分化，导致COPD患者骨骼肌耐力下降。

线粒体ROS的增加也能干扰骨骼肌分化。过量的线粒体ROS能够激活NF-κB上调钙离子结合蛋白S100B，从而激活NF-κB/Ying Yang 1轴负向调节miR-133，导致棕色脂肪生成因子PR结构域蛋白16（PR domain-containing 16，PRDM-16）积累，上调骨形态发生蛋白表达，减少成肌细胞形成，导致成肌细胞转变为棕色脂肪细胞[77]。有研究发现，COPD患者S100B水平上升，提示可能存在成肌细胞细胞分化失败，但对COPD患者骨骼肌的影响仍需进一步探讨[78]。高浓度的线粒体ROS还能降低抗氧化剂谷胱甘肽水平，激活NF-κB通路引起MyoD表达减少，影响成肌细胞分化效率，导致成肌细胞功能丧失[79]。TESTELMANS等[80]研究发现NF-κB的激活可导致COPD患者骨骼肌中MyoD表达降低，影响Ⅰ型肌纤维分化，造成肌肉抗疲劳性降低。

综上，异常的线粒体自噬、失活的线粒体生物发生因子PGC-1α及相关通路和激增的线粒体ROS均能引起肌源性分化异常，降低成肌细胞分化效率，导致骨骼肌棕色脂肪细胞增多和Ⅰ型肌纤维比例降低，造成骨骼肌氧化能力下降。在中、重度的COPD状态下，氧化应激加速骨骼肌的分解，其消耗大于增长且伴随分化异常，从而引起骨骼肌功能障碍。线粒体ROS作为氧化应激的主要来源起关键作用，导致富含线粒体的Ⅰ型肌纤维相较于Ⅱ型肌纤维受到的影响更大。COPD患者骨骼肌线粒体呼吸链受损、线粒体自噬激增和生物发生减少，其中线粒体呼吸链的受损导致线粒体ROS急剧升高，打破氧化和抗氧化平衡引起氧化应激，不但会加快骨骼肌降解和减少骨骼肌生成，还会干扰骨骼肌分化，加重骨骼肌功能障碍。此外，线粒体ROS还会影响线粒体自噬和生物发生过程，形成恶性循环。

3 运动康复训练对COPD骨骼肌线粒体损伤的潜在影响

运动康复训练作为一种常规康复手段，是COPD患者骨骼肌功能障碍最有效的非药物干预措施[81]，其主要的机制可能与改善线粒体损伤有关。

3.1 运动康复训练可修复COPD患者骨骼肌线粒体呼吸链

COPD患者骨骼肌存在线粒体呼吸链破坏，而运动康复可以修复受损的线粒体呼吸链，加快ROS清除和ATP合成，减轻骨骼肌氧化应激和恢复持续性肌肉供能。BRØNSTAD等[82]通过6周的高强度间歇有氧伸膝运动训练，发现COPD患者股外侧肌最大线粒体呼吸速率和柠檬酸合酶活性增加，骨骼肌峰值功率和氧化能力明显升高；运动康复训练通过增加线粒体质量和提高复合体Ⅰ活性，改善COPD患者线粒体呼吸能力，提示运动康复训练可以恢复受损的线粒体呼吸链，进而改善骨骼肌功能障碍。运动康复训练还能诱导COPD患者线粒体氧化磷酸化，提高二磷酸腺苷（adenosine diphosphate，ADP）水平和促进ATP生成，为骨骼肌提供更多能量[83]。CALVERT等[84]研究发现，经过7周耐力和力量训练后，COPD患者血氨水平、乳酸积累和腺嘌呤核苷酸丢失减少，ATP合成增加，骨骼肌持续性供能明显改善。在改善氧化应激方面，运动康复训练可改善解偶联蛋白3水平，减少COPD患者线粒体ROS生成，保护线粒体免受脂质过氧化毒性作用影响，提高骨骼肌氧化能力[85]。因此，运动康复训练可能通过修复线粒体呼吸链加快ROS清除和诱导线粒体氧化磷酸化，减轻骨骼肌氧化应激并持续性供能。

3.2 运动康复训练可调控COPD患者骨骼肌线粒体自噬

COPD患者骨骼肌中线粒体自噬水平升高，但仍不足以及时清除受损线粒体，以维持正常生理功能。运动康复可以改善线粒体自噬水平，加快线粒体重塑，诱导骨骼肌发生适应性变化。有研究显示，肌肉收缩能够维持COPD小鼠肌管中线粒体自噬关键蛋白Parkin正常水平，以防止MHC减少，即使是在烟雾暴露的情况下也能上调Parkin促进MHC表达，提示运动通过改善线粒体自噬预防COPD导致的肌肉减少[20]。运动康复训练还能调节其他自噬相关蛋白水平，诱导线粒体自噬发生，维持线粒体平衡，促进骨骼肌质量和功能恢复[86]。但值得注意的是，运动康复训练对线粒体自噬的调节也会影响线粒体生物发生。在Parkin缺失的情况下，运动

康复训练通过增加Parkin相互作用底物的核定位以及减少PGC-1α表达,影响线粒体自噬和生物发生过程,降低线粒体含量和密度,导致骨骼肌氧化能力下降[87]。因此,运动康复训练可能通过上调以Parkin为代表的自噬相关蛋白表达,促进线粒体自噬,增加肌球蛋白以抑制肌肉萎缩,从而提高骨骼肌质量。

3.3 运动康复训练可促进COPD患者骨骼肌线粒体生物发生

COPD患者骨骼肌常存在线粒体生物发生减少的现象,运动康复能够增加线粒体生物发生,改善线粒体完整性,加快骨骼肌合成并提高骨骼肌氧化能力。有研究显示,运动康复可上调COPD患者骨骼肌中PGC-1α mRNA水平,促进骨骼肌质量增加和功能改善[7]。此外,运动康复训练还能够激活AMPK/PGC-1α通路,提高PGC-1α蛋白表达,增加线粒体生物发生和减少ROS产生,加强骨骼肌合成[38]。在这个过程中,PGC-1α的激活可促进线粒体转录因子A表达,阻止mtDNA降解并加快线粒体蛋白转录,改善骨骼肌萎缩[88]。运动康复训练还可激活PGC-1α下游因子Nrf2增强机体抗氧化水平,提高骨骼肌有氧能力[89]。因此,运动康复训练可能通过上调PGC-1α水平增加线粒体生物发生,促进骨骼肌合成并改善骨骼肌抗氧化水平。

4 小结与展望

骨骼肌功能障碍是COPD患者常见的并发症之一,这将导致患者运动能力下降,加重疾病恶化。线粒体作为维持骨骼肌正常运作的重要细胞器,其损伤将造成骨骼肌收缩无力,引起氧化应激和表观遗传学的改变。线粒体损伤是造成COPD患者骨骼肌功能障碍的主要驱动机制,表现为线粒体呼吸链受损、自噬增多和生物发生减少,通过增加骨骼肌降解、减少骨骼肌生成和干扰骨骼肌分化,影响骨骼肌结构、功能和代谢。运动康复训练可通过改善异常的线粒体自噬水平、促进线粒体生物发生和修复受损的线粒体呼吸链,以缓解线粒体损伤,防止COPD患者骨骼肌功能障碍。但是现有研究仍无法为线粒体损伤与COPD骨骼肌生成降低、骨骼肌分化异常提供直接有力的支持,也缺乏针对线粒体损伤导致的COPD骨骼肌质量和功能改变的分子机制相关研究。此外,运动康复训练是如何改善COPD骨骼肌线粒体自噬、生物发生和呼吸链损伤,从而提高骨骼肌功能的作用机制尚未形成统一共识。后续研究仍需进一步探讨线粒体对维持骨骼肌正常功能结构的关键作用、COPD骨骼肌功能障碍的发生原理以及运动康复训练调节线粒体损伤改善COPD骨骼肌功能障碍的具体作用机制,以期为运动康复训练干预COPD骨骼肌功能障碍提供参考依据。

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Effect of Exercise Rehabilitation Training Regulating Mitochondrial Damage on Skeletal Muscle Dysfunction in Chronic Obstructive Pulmonary Disease

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ABSTRACT Chronic obstructive pulmonary disease (COPD) is a heterogeneous chronic respiratory condition, and skeletal muscle dysfunction is one of its common complications, mainly clinically manifested as decreased muscle strength and endurance, altered muscle fiber type and decreased skeletal muscle mass. Mitochondrial damage is one of the key factors causing skeletal muscle dysfunction. Mitochondria not only provide energy for skeletal muscle, but also participate in reactive oxygen species (ROS) production, autophagy and protein turnover, which is of great significance to maintain the normal function of skeletal muscle. This study elucidated the mitochondrial changes in skeletal muscle dysfunction in patients with COPD, the mechanism of mitochondrial damage in skeletal muscle dysfunction in patients with COPD, and the potential effects of exercise rehabilitation training on mitochondrial damage in skeletal muscle in patients with COPD, in order to further clarify the relationship between mitochondria and skeletal muscle function, and to provide a reference for optimizing the exercise rehabilitation program for skeletal muscle dysfunction in COPD. The mitochondrial changes of skeletal muscle dysfunction in COPD mainly include impairment of the mitochondrial respiratory chain, a surge in mitochondrial autophagy, and a decreased in mitochondrial biogenesis. The mechanisms underlying mitochondrial damage of skeletal muscle dysfunction in COPD mainly include increasing skeletal muscle degradation, decreasing of skeletal muscle production and interfering with skeletal muscle differentiation. The potential effects of exercise rehabilitation training regulating mitochondrial damage in COPD skeletal muscle mainly include repairing the respiratory chain of skeletal muscle mitochondria in COPD patients, regulating mitophagy of skeletal muscle mitochondria, and promote the mitochondrial biogenesis of skeletal muscle in patients with COPD. Future research still needs to explore the key role of mitochondria in maintaining the normal functional structure of skeletal muscle, the mechanism of COPD skeletal muscle dysfunction, and the specific mechanism of exercise rehabilitation training in regulating mitochondrial damage to improve COPD skeletal muscle dysfunction, so as to provide a reference for exercise rehabilitation training in COPD skeletal muscle dysfunction.

KEY WORDS chronic obstructive pulmonary disease; skeletal muscle dysfunction; mitochondrial damage; mitophagy; exercise rehabilitation training
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