· 综述 ·

线粒体动力学失衡与新型冠状病毒感染相关急性呼吸窘迫综合征的研究进展

张子佳[1]　杜斌[1]　吴逊尧[1]　胡晓芸[2]　刁世童[1]　董润[1]

[1] 北京协和医院 MICU，北京 100010；[2] 北京协和医院重症医学科，北京 100010

通信作者：杜斌，Email：dubin98@gmail.com

【摘要】 新型冠状病毒（新冠病毒）感染所致重症肺炎患者常合并急性呼吸窘迫综合征（ARDS），病死率高。ARDS 以弥漫性肺泡损伤、肺水肿和低氧血症为特征，线粒体在低氧和病毒感染下易出现形态及功能异常，进而引发细胞凋亡和损伤，严重影响疾病进程。线粒体通过裂变和融合维持稳态，ARDS 时低氧使动力相关蛋白 1（Drp1）磷酸化，引发线粒体过度分裂，破坏肺泡上皮屏障。动物实验显示抑制该过程可减轻肺损伤，为治疗提供潜在方向。新冠病毒感染相关 ARDS 的病理机制与典型 ARDS 类似，但程度更严重，病毒感染和低氧导致线粒体平衡被打破，引发裂变和自噬异常，促使氧化应激和线粒体 DNA（mtDNA）释放，激活炎症小体，诱导缺氧诱导因子 -1α（HIF-1α）表达，加剧病毒感染、炎症和凝血反应，导致多器官损伤。针对新冠病毒感染相关 ARDS 的治疗常使用机械通气和糖皮质激素。机械通气易导致肺和膈肌损伤、线粒体动力学改变，肺保护性通气策略可减少不良影响；糖皮质激素可调节线粒体功能和免疫反应，通过多途径改善病情。新冠病毒感染相关线粒体动力学失衡源于低氧和病毒蛋白，引发肺部及多器官损伤。本综述旨在明确线粒体动力学失衡与新冠病毒感染相关 ARDS 的病理生理学机制，探索调控线粒体动力学平衡以治疗该疾病的有效策略，为新冠病毒感染相关 ARDS 患者提供新的治疗靶点与方法。由于现有治疗有局限，未来需深入研究线粒体功能障碍机制，开发新疗法和调控策略，以提升治疗效果。

【关键词】 线粒体动力学；　新型冠状病毒感染；　急性呼吸窘迫综合征

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Research progress on the relationship between mitochondrial dynamics imbalance and novel coronavirus infection-related acute respiratory distress syndrome

Zhang Zijia[1], Du Bin[1], Wu Xunyao[1], Hu Xiaoyun[2], Diao Shitong[1], Dong Run[1]

[1]MICU, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing, 100010, China; [2]Department of Critical Care Medicine, Peking Union Medical College Hospital, Beijing, 100010, China

Corresponding author: Du Bin, Email: dubin98@gmail.com

【Abstract】 Patients with severe pneumonia caused by novel coronavirus infection are often complicated with acute respiratory distress syndrome (ARDS), which has a high mortality. ARDS is characterized by diffuse alveolar damage, pulmonary edema, and hypoxemia. Mitochondria are prone to morphological and functional abnormalities under hypoxia and viral infection, which can lead to cell apoptosis and damage, severely impacting the disease progression. Mitochondria maintain homeostasis through fission and fusion. In ARDS, hypoxia leads to the phosphorylation of dynamin-related protein 1 (Drp1), triggering excessive mitochondrial fission and damaging the alveolar epithelial barrier. Animal experiments have shown that inhibiting this process can alleviate lung injury, providing a potential direction for treatment. The pathology of novel coronavirus infection-related ARDS is similar to that of typical ARDS but more severe. Viral infection and hypoxia disrupt the mitochondrial balance, causing fission and autophagy abnormalities, promoting oxidative stress and mitochondrial DNA (mtDNA) release, activating inflammasomes, inducing the expression of hypoxia-inducible factor-1α (HIF-1α), exacerbating viral infection, inflammation, and coagulation reactions, and resulting in multiple organ damage. Mechanical ventilation and glucocorticoids are commonly used in the treatment of novel coronavirus infection-related ARDS. Mechanical ventilation is likely to cause lung and diaphragm injuries and changes in mitochondrial dynamics, while the lung protective ventilation strategy can reduce the adverse effects. Glucocorticoids can regulate mitochondrial function and immune response and improve the patient's condition through multiple pathways. The mitochondrial dynamics imbalance in novel coronavirus infection-related ARDS is caused by hypoxia and viral proteins, leading to lung and multiple organ injuries. To clarify the pathophysiological mechanism of mitochondrial dynamics imbalance in novel coronavirus infection-related ARDS and explore effective strategies for regulating mitochondrial dynamics balance to treat this disease, so as to provide new treatment targets and methods for patients with novel coronavirus infection-related ARDS. The existing treatments have limitations. Future research needs to deeply study the mechanism of mitochondrial dysfunction, develop new therapies and regulatory strategies, and improve the treatment effect.

【Key words】 Mitochondrial dynamics; Novel coronavirus infection; Acute respiratory distress syndrome
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急性呼吸窘迫综合征(acute respiratory distress syndrome, ARDS)是重症新型冠状病毒(新冠病毒)感染患者最常见的并发症,发生率为30%~60%,病死率达50%~70%[1],其特征为弥漫性肺泡损伤、持续炎症反应刺激、肺泡-毛细血管屏障损伤和肺水肿,临床表现为严重的低氧血症和双侧肺浸润,最终导致呼吸衰竭[2-3]。线粒体是动态的细胞器,不断经历融合/裂变以维持正常的细胞生理活动和能量代谢。低氧和病毒感染均可以诱发线粒体动力学的失衡,继而诱发线粒体自噬异常、氧化应激和能量代谢紊乱,最终导致细胞的凋亡和损伤。因此,本文将以线粒体动力学失衡为切入点,系统阐述新冠病毒感染相关ARDS继发的线粒体动力学失衡所导致的肺部疾病及肺损伤的机制,并探索重症新冠病毒感染相关ARDS的新治疗靶点及策略。

1 线粒体动力学与ARDS

线粒体是细胞进行有氧呼吸和能量代谢的重要场所,被称为"能量工厂",也是缺血缺氧后即刻发生损伤的细胞器之一。线粒体在细胞内并非静止不动,而是通过不断地裂变和融合,维持自身功能的完整性,并适应细胞内的能量需求,即线粒体动力学[4]。线粒体的分裂、融合和转运过程失去平衡时,可导致线粒体形态、数量、分布及功能异常,发生线粒体动力学失衡[5]。线粒体的动力学平衡对于维持线粒体的质量和功能起重要作用。线粒体融合可增加线粒体嵴的重塑并维持线粒体网络的稳定,融合过程主要由视神经萎缩蛋白1(optic atrophy 1, OPA1)和线粒体融合蛋白(mitochondrial fusion proteins, Mfn1、Mfn2)参与[6];线粒体分裂可调节细胞代谢和能量供应,主要由动力相关蛋白1(dynamin-related protein 1, Drp1)调控[7]。

ARDS是一种急性弥漫性炎症性肺损伤,由于严重感染、休克、创伤等因素导致肺泡毛细血管膜损伤和通透性增加,引起肺水肿和肺不张,从而导致通气肺组织减少。肺泡-毛细血管屏障功能损伤是ARDS的重要病理生理学特征,其临床表现为顽固性低氧血症和进行性呼吸窘迫。线粒体作为细胞的主要耗氧细胞器,主要通过氧化磷酸化产生三磷酸腺苷(adenosine triphosphate, ATP)供能。当细胞内处于持续低氧条件下时,ATP的生成减少,细胞会启动代偿机制,如增强糖酵解途径,产生较少的ATP,并伴随乳酸等副产物的增加。低氧会通过抑制氧化磷酸化调控线粒体动力学平衡、破坏线粒体的完整性,并诱导Ⅱ型肺泡上皮细胞发生凋亡[8-9]。此外,肺内外致病因素可通过引发炎症反应促使肺泡上皮细胞形成不利的内环境,导致线粒体自噬功能紊乱,而过度的线粒体自噬激活可加重炎症反应[10]。低氧环境会使Drp1磷酸化水平增加,促进线粒体发生过度分裂,磷酸化的Drp1同时被招募到线粒体内膜上形成多聚螺旋结构,收缩挤压线粒体呈现片段化,使细胞功能受损甚至发生死亡[11]。脂多糖(lipopolysaccharide, LPS)通过诱导Drp1蛋白在Ser616位点发生磷酸化,激活Drp1介导的线粒体超分裂,促进肺泡上皮间紧密连接结构破坏和上皮细胞凋亡,破坏肺上皮屏障的完整性[12]。基于ARDS小鼠模型的研究显示,抑制Drp1介导的线粒体分裂可以显著减轻ARDS肺泡上皮细胞损伤和功能破坏,提示ARDS患者的肺泡上皮细胞发生线粒体动力学失衡,或可作为临床治疗的潜在靶点[13]。

2 线粒体动力学失衡与新冠病毒感染相关ARDS

2.1 新冠病毒感染相关ARDS:弥漫性肺泡损伤及急性纤维素性机化性肺炎是新冠病毒感染相关ARDS的病理基础。新冠病毒感染相关ARDS与典型ARDS相似,组织病理学特征均为弥漫性肺泡损伤,伴肺泡扩张和塌陷、透明膜形成、间质性水肿、毛细血管充血以及Ⅱ型肺细胞丢失[14];但新冠病毒感染相关ARDS患者可见肺部微血栓明显增加[15],由于急进性的肺纤维化,表现出更严重的低氧血症和更高的病死率[16]。有研究表明,新冠病毒感染相关ARDS患者低氧血症及肺内分流的严重程度常与肺顺应性下降程度不匹配,这与典型ARDS有所不同[17]。新冠病毒感染相关ARDS通常伴随高水平的循环炎症因子,如肿瘤坏死因子-α(tumor necrosis factor-α, TNF-α)和白细胞介素-6(interleukin-6, IL-6),这可能是导致新冠病毒感染相关ARDS的原因[18]。这种炎症因子风暴不仅限于肺部,还涉及全身性炎症反应,包括血管内皮损伤、广泛微血栓形成和肺毛细血管增生[19-20]。

2.2 线粒体动力学失衡与新冠病毒感染相关ARDS的肺功能障碍和损伤:病毒感染宿主细胞后,会打破线粒体动力学平衡,引发线粒体裂变和诱导线粒体自噬异常。例如,乙型肝炎病毒(hepatitis B virus, HBV)抑制线粒体融合,通过诱导E3泛素化连接酶Parkin促进线粒体融合蛋白2(mitofusin 2, Mfn2)的泛素化及降解;另一方面诱导Drp1磷酸化促进线粒体裂变,介导线粒体动力学异常[21]。流感病毒PR8株感染可以导致线粒体片段受损,诱导线粒体自噬,加速线粒体碎裂[22]。委内瑞拉马脑脊髓炎病毒(Venezuelan equine encephalomyelitis virus, VEEV)感染的细胞中会出现Drp1蛋白富集,线粒体分裂抑制剂1(mitochondrial division inhibitor 1, Mdivi-1)可以显著降低天冬氨酸特异性半胱氨酸蛋白酶(caspase)裂解,从而支持线粒体裂变是VEEV感染细胞凋亡的因素,提示VEEV感染可能也是通过诱发Drp1蛋白介导的线粒体裂变促进感染细胞的凋亡[23]。寨卡病毒(Zika virus, ZIKV)的非结构蛋白NS4A蛋白过表达后会诱导Drp1蛋白的转录后修饰和磷酸化,引起线粒体裂变,加重线粒体碎片化[24]。

新冠病毒的Spike蛋白或灭活新冠病毒体外刺激的小胶质细胞呈现出线粒体形态改变以及线粒体的碎片化,说明新冠病毒也可以引起被感染宿主细胞的动力学失衡[25-26]。

线粒体动力学失衡会继发线粒体自噬、氧化应激并诱导线粒体 DNA（mitochondrial DNA，mtDNA）释放，加重肺部损伤和肺功能障碍。新冠病毒感染后引起线粒体动力学失衡，并调控线粒体自噬相关蛋白（如 p62 与 LC3 蛋白）的结合和 Spike 蛋白的表达，使宿主细胞线粒体自噬功能发生损伤，从而促进自身病毒的持续复制和 IL-18 表达的增加及新冠病毒感染相关心肺炎症反应[27-28]。新冠病毒相关蛋白可以促进线粒体氧化应激，线粒体活性氧（mitochondrial reactive oxygen species，mtROS）水平升高[29-31]，然而，干扰新冠病毒诱导的线粒体氧化应激可以显著降低内皮功能障碍[32]。新冠病毒的非结构蛋白 4（nonstructural protein 4，NSP4）和开放阅读框蛋白 9b（open reading frame 9b，ORF9b）诱导形成外膜微孔结构并增加 mtDNA 的释放，mtDNA 进一步活化 NOD 样受体蛋白 3（NOD-like receptor protein 3，NLRP3）炎症小体复合物，介导 caspase-1 依赖的炎症细胞因子释放，诱导线粒体碎片化、钙失衡及细胞凋亡，从而引起线粒体动力学失衡及功能紊乱，这可能是引起新冠病毒感染相关 ARDS 患者“细胞因子风暴”的重要机制[33-36]。相应的，新冠病毒感染患者血清 mtDNA 含量较健康对照者增加，并激活 Toll 样受体 9（Toll-like receptors 9，TLR9）信号转导，促进炎症反应及内皮功能障碍[37]。在构建的新冠病毒感染的人血管紧张素转换酶 2（angiotensin-converting enzyme 2，ACE2）转基因小鼠模型中，通过抑制 TLR 诱导的 mtDNA 合成，在体外和体内阻断 NLRP3 炎症小体活化，ARDS 症状显著减轻[38]。

新冠病毒感染相关 ARDS 中的低氧环境可触发一系列细胞内信号转导，导致缺氧诱导因子 -1α（hypoxia-inducible factor-1α，HIF-1α）的表达。新冠病毒的 ORF3a 诱导线粒体损伤和 mtROS 释放，也可以促进 HIF-1α 的表达[39-40]。在新冠病毒感染相关 ARDS 患者中，HIF-1α 可以通过促进新冠病毒的持续感染，触发或增强炎症因子风暴，减少中性粒细胞凋亡，从而造成肺组织局部损伤及多器官损伤的发生，可能是新冠病毒感染相关 ARDS 患者治疗的一个潜在、重要的分子治疗靶点及信号通路[41]。mtROS/HIF-1α 信号促进单核细胞和肺泡巨噬细胞的糖酵解过程，而糖酵解也进一步促进新冠病毒持续复制、乳酸释放和炎症因子风暴，导致免疫细胞功能障碍及肺上皮细胞凋亡，促进新冠病毒感染相关 ARDS 的疾病进展[42-44]。此外，HIF-1α 还可以通过影响凝血因子和凝血酶原复合物的功能，导致新冠病毒感染相关 ARDS 患者发生凝血级联反应及微血栓形成，最终导致多器官损伤[45-46]。

3　线粒体动力学平衡与新冠病毒感染相关 ARDS 的治疗

目前新冠病毒感染相关 ARDS 的治疗手段主要包括机械通气（mechanical ventilation，MV）和药物治疗。MV 通过提供足够的氧气和排出二氧化碳，改善患者的氧合状态，减轻呼吸肌疲劳，为患者提供必要的呼吸支持，减少肺损伤，改善肺功能[47]。在药物治疗方面，糖皮质激素在新冠病毒感染相关 ARDS 治疗中的应用尤为广泛，可以通过抑制炎症反应和减少“细胞因子风暴”来发挥作用[48]。

3.1　MV 与线粒体动力学平衡：新冠病毒感染相关 ARDS 的病理生理变化导致严重低氧血症和肺顺应性降低，需要 MV 支持，常联合俯卧位通气和体外膜肺氧合（extracorporeal membrane oxygenation，ECMO）治疗[49-51]。但 MV 本身也可能导致肺损伤及膈肌萎缩和收缩功能障碍，即 MV 相关性肺损伤（ventilation-induced lung injury，VILI）和 MV 相关性膈肌功能障碍（ventilation-induced diaphragmatic dysfunction，VIDD），均是 MV 常见的并发症[52]。在 MV 的情况下，膈肌和肺组织的线粒体动力学可能因周期性的氧环境变化发生改变。研究表明，MV 6 h 后大鼠横膈膜线粒体外膜的超微亚结构改变，并发生线粒体碎片化，Mfn2 和 OPA1 的表达无变化，而 Drp1 蛋白的表达水平显著增加[53]。MV 6 h 后，大鼠横膈膜组织的蛋白组学测序结果显示，线粒体功能相关的通路和蛋白存在差异表达，其中 Drp1 蛋白处于上调差异蛋白的前列；电镜结果显示，线粒体结构出现碎片化，线粒体裂变能力增加，而过度的线粒体分裂继发 mtROS 产生和线粒体功能障碍[54]。同时，MV 诱发的线粒体超分裂会引起线粒体自噬的过度活化和肌浆网钙泄漏，引起膈肌损伤[55-56]。高潮气量 MV 诱导的机械过度拉伸激活内质网通道蛋白 IP3 受体 1（IP3 receptor 1，IP3R1），而 IP3R 相关的 Ca^{2+} 失调导致内质网应激和线粒体功能障碍，诱导 NLRP3 炎症小体激活，导致 VILI[57]。MV 可导致线粒体动力学失衡并诱导 HIF-1α 的表达上调，也可能是参与促进新冠病毒持续复制、炎症因子风暴和多器官损伤的部分机制[58]。MV 也可导致肺部线粒体功能障碍和肺泡化延迟，通过激活特定的信号通路，导致线粒体功能障碍和肌肉萎缩[59]。因此，应在临床治疗中采用肺保护性通气策略，如降低潮气量、限制平台压力和使用适当的呼气末正压（positive end-expiratory pressure，PEEP），可以减少 VILI 的发生及对线粒体动力学平衡的不良影响，改善患者的临床结局。

3.2　糖皮质激素与线粒体动力学平衡：糖皮质激素作为治疗重症新冠病毒感染相关 ARDS 的重要药物之一，其作用机制包括抑制炎症反应和调节免疫系统[60]。糖皮质激素能够抑制炎症细胞（如中性粒细胞、巨噬细胞和淋巴细胞）的活性，并抑制促炎细胞因子（如 TNF 和 IL）的产生，从而减轻炎症因子风暴[61]。糖皮质激素还可以通过调节免疫细胞的功能，如减少 T 细胞的活化和增殖，进一步控制炎症反应[62]。而线粒体动力学平衡的调节也可能与糖皮质激素相互作用。糖皮质激素可以通过影响线粒体的分裂和融合过程，间接调节线粒体功能，减轻炎症反应[63]。糖皮质激素通过影响线粒体内的信号转导途径，如哺乳动物雷帕霉素靶蛋白（mammalian target of rapamycin，mTOR）、AMP 活化蛋白激酶（AMP-activated protein kinase，AMPK）、核转录因子 -κB（nuclear factor-κB，NF-κB）和其他炎症信号通路的激活，调节线粒体的代谢状态和自噬过程，进一步减轻线粒体功能障碍，减少炎症介质的产生，从而减轻炎症反应，改善新冠病毒感染相关 ARDS 患者的病情，降低病死率[48, 64]。糖皮质激素可通过抑制肺组织 NF-κB 活性，下调巨噬细胞炎症蛋

白 -1α（macrophage inflammatory protein-1α，MIP-1α）的表达，从而减轻肺损伤程度[65]。糖皮质激素能够直接抑制单核细胞趋化蛋白 -1（monocyte chemoattractant protein-1，MCP-1）信使 RNA（messenger RNA，mRNA）的表达，减轻肺泡炎症反应和肺纤维化程度[66]。糖皮质激素还能够通过影响 TLR 介导的信号转导途径来调节免疫细胞活性。例如，新冠病毒的刺突蛋白可能通过与 TLR4 结合并激活其信号转导，增加细胞表面 ACE2 的表达，从而促进病毒进入宿主细胞[67]。而糖皮质激素能够抑制 TLR2 和 TLR4 介导的炎症途径，减少炎症细胞因子的产生[68]。由此可见，糖皮质激素在治疗新冠病毒感染相关 ARDS 中的作用机制是多方面的，包括抑制炎症反应、调节免疫细胞功能以及影响线粒体动力学，并通过调节细胞信号转导途径影响因子释放，改善患者“细胞因子风暴”导致的临床症状，减轻病情严重程度，促进患者恢复。

4 总结与展望

线粒体动力学中分裂与融合的平衡对于维持细胞的正常生理活动起关键作用。新冠病毒感染相关 ARDS 的线粒体动力学失衡，一方面，由于严重的低氧血症引起的 Drp1 介导线粒体超分裂；另一方面，新冠病毒的蛋白成分也与线粒体相互作用，介导线粒体功能紊乱，并引起肺损伤和肺功能障碍。

目前，现有的治疗手段仍存在局限性。MV 可能加重肺损伤及膈肌损伤，导致 VILI 及 VIDD，不恰当的 MV 策略也可能导致高病死率。糖皮质激素可能会引起免疫抑制（immunosuppression，IS）作用，延缓病毒清除，以及导致神经系统和代谢紊乱、继发感染等不良反应的发生。未来的研究可侧重于通过分子生物学和细胞生物学方法，明确线粒体功能障碍如何影响新冠病毒感染的病理过程，以及如何通过调节线粒体功能来减轻病毒引起的肺损伤，并基于线粒体在新冠病毒感染相关 ARDS 中的作用，开发新的治疗药物或疗法，如线粒体靶向抗氧化剂、调节线粒体通透性孔蛋白活性的药物等，以减轻炎症反应和氧化应激，保护肺组织。研究现有的抗病毒、抗炎和免疫调节治疗策略对线粒体功能的影响，以及这些治疗策略是否能够通过改善线粒体功能来提高治疗效果，以期为新冠病毒感染相关 ARDS 提供新的治疗思路。虽然线粒体动力学和线粒体自噬有希望成为 IS 的新靶点，但是如何实现线粒体动力学中分裂与融合的平衡以及如何发挥线粒体自噬“双刃剑”中“利”的一面，仍需更加深入地探索研究。

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