

• 综述 •

线粒体融合和裂变在呼吸系统疾病中的研究进展

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[摘要] 线粒体是多细胞生命不可缺少的组成部分, 通过融合和裂变进行形态上的变化和空间上的重新排列以适应细胞的需求, 维持能量平衡, 这个过程称为线粒体动力学。大量研究表明线粒体通过融合和裂变参与细胞凋亡、细胞增殖、细胞迁移、能量代谢等多种细胞生物学过程。近年来呼吸系统疾病成为全球主要的健康问题。最新的研究发现线粒体动力学障碍在许多呼吸系统疾病的发生发展过程中起重要作用, 研究线粒体动力学障碍为呼吸系统疾病形成机制提供新的视野。

[关键词] 肺疾病; 线粒体; 线粒体动力学; 融合; 裂变

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Research progress of mitochondrial fusion and fission in respiratory diseases development

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[Abstract] Mitochondria are an indispensable component of multicellular life. They undergo morphological changes and spatial rearrangement to meet the needs of cells and maintain energy balance through fusion and fission, a process called mitochondrial dynamics. A large number of studies have shown that mitochondria participate in a variety of cell biological processes such as apoptosis, cell proliferation, cell migration, and energy metabolism through fusion and fission. In recent years, respiratory diseases have become a major global health problem. Recent studies have found that mitochondrial dynamics disorder plays an important role in the formation of many respiratory diseases. The study of mitochondrial dynamics disorders provides a new perspective for the formation mechanism of respiratory diseases.

[Key words] pulmonary disease; mitochondria; mitochondrial dynamics; fusion; fission

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线粒体是一种独特的细胞器, 由线粒体外膜 (outer mitochondrial membrane, OMM)、线粒体内膜 (inner mitochondrial membrane, IMM) 和线粒体基质组成。OMM 多孔, 允许离子和不带电的小分子通过。IMM 由电子传递系统、三磷酸腺苷 (adenosine 5'-triphosphate, ATP) 合酶和转运蛋白的复合物组

成^[1]。线粒体基质中含有 13 个结构基因的线粒体 DNA (mitochondrial DNA, mtDNA)^[2], 这些基因编码线粒体电子传递链 (electron transport chain, ETC) 复合物 I、III、IV 和 V 所必需的亚基, 产生 ATP, 基质中还含有在三羧酸循环中参与氧化磷酸化的关键酶^[3]。线粒体作为哺乳动物细胞动力源, 是促进分解代谢、释放能量的工厂^[4]。除能量代谢以外, 线粒体还参与钙代谢、凋亡、程序性死亡等细胞过程^[5]。从 ATP 生成到免疫激活等细胞活动的重要过程都离不开线粒体的调节^[6]。

线粒体功能的核心是线粒体动力学^[7], 是线粒

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体通过融合和裂变保持动态平衡的过程^[8],与线粒体的功能密切相关^[9]。在生理条件下,线粒体融合和裂变的动态平衡,不仅可以维持线粒体的大小和形状,还可维持线粒体的总体分布^[10]。当线粒体功能异常时,线粒体的运动性和延伸率会降低^[11]。线粒体融合使线粒体延伸成相互连接的管状网络,导致其内容物(即代谢物、蛋白质和 mtDNA)混合和能量重新分配^[12],可防止功能失调线粒体的局部积累^[13]。相反,线粒体裂变是一个将管状网络分裂成更小、离散的细胞器的过程^[14]。裂变可促进受损线粒体与正常线粒体的分离,以维持整个线粒体的正常功能^[15]。线粒体融合通过转移基因产物影响线粒体功能,裂变可维持线粒体适当的数量和分布^[16],线粒体融合和裂变的动态平衡在维持线粒体功能中起着重要作用^[17]。

研究表明,线粒体融合和裂变的缺陷导致的线粒体功能障碍参与了肺水肿、肺动脉高压、慢性阻塞性肺疾病(chronic obstructive pulmonary disease, COPD)、特发性肺纤维化和新型冠状病毒肺炎等疾病的发生^[18],靶向线粒体的研究可能有助于发现呼吸系统疾病新的治疗方法。

1 线粒体融合和裂变的分子机制

1.1 线粒体融合的分子机制

线粒体融合是两个线粒体的结合,以形成一个相互紧密连接的线粒体网络^[19]。线粒体融合是真核细胞中必不可少的生理事件,因为它促进脂质和蛋白质的交换、mtDNA 的融合以及对线粒体自噬的抵抗^[20]。线粒体融合相关蛋白在维持线粒体完整性和功能方面起着至关重要的作用。这些蛋白包括调节 IMM 融合的视神经萎缩蛋白 1(optic atrophy 1, OPA1),以及调节 OMM 融合的 Mitofusin1/2(MFN1/2)^[21]。融合过程从两个 MFN1 分子的对接开始,线粒体构象变化,从而驱动 MFN1 水解 GTP,导致 OMM 融合。同一个线粒体中的 MFN 蛋白之间形成聚合物,介导线粒体融合,相邻线粒体的 MFN 蛋白之间形成聚合物,以增加相邻线粒体之间的表面接触,为线粒体融合做准备^[22]。OMM 融合后,紧接着由 OPA1 调节 IMM 的融合,但其调节线粒体形态的分子机制尚不清楚^[23]。MFN1 和 MFN2 介导融合方面的功能相似,但 MFN2 还有其他作用:一方面,一些研究认为 MFN2 作为内质网和线粒体之间的桥梁,促进线粒体钙摄取和线粒体膜电位($\Delta\Psi_m$)的调节^[24];另一方面,有研究提出 MFN2 的作用是防止内质网和线粒

体之间过度接近,从而防止细胞毒性。关于 MFN2 在线粒体融合中的作用需要进一步的研究来充分阐明^[25]。

1.2 线粒体裂变的分子机制

线粒体裂变是 1 个线粒体分裂成 2 个或多个较小线粒体的过程,是进行线粒体自噬、mtDNA 复制以及细胞分裂过程中线粒体再分布所必需的^[26]。线粒体裂变由大量分子形成复杂、精确的调控,其中动力蛋白相关蛋白 1(dynamamin-related protein 1, Drp1)及其抑制剂(mitochondrial division inhibitor 1, Mdivi-1)、线粒体分裂蛋白 1(mitochondrial fission protein 1, Fis1)和线粒体分裂因子(mitochondrial fission factor, MFF)是裂变分子机制的中心组成部分^[21]。Drp1 在 Ser616 位点的磷酸化促进线粒体分裂,而在 Ser637 位点的磷酸化则抑制线粒体分裂^[27]。当线粒体受损时,Drp1 被募集到 OMM,但它不是直接与 OMM 结合,而是与 OMM 上的适配蛋白 Fis1 和 MFF 形成复合物,通过 GTP 的水解和 Drp1 螺旋结构的收缩,OMM 的完整性被破坏,开始了裂变过程^[20]。Mdivi-1 的作用是通过结合 1 个变构位点,选择性地靶向抑制 Drp1 催化 GTP 水解和组装成线粒体环状结构的能力,Mdivi-1 可诱导线粒体快速可逆融合,但不影响细胞骨架和内质网的结构与功能^[27]。目前为止,调节 Drp1 募集和激活的机制尚不完全清楚。有研究发现,非肌肉肌球蛋白 II 是由 2 条重链和 4 条轻链组成的多聚体蛋白复合物,与肌动蛋白共同作用,产生机械力并诱导线粒体裂变部位的预收缩,促进 Drp1 招募和激活^[28]。

2 线粒体融合和裂变与呼吸系统疾病

2.1 肺动脉高压(pulmonary hypertension, PH)

PH 是一种由不同病因引起的平均肺动脉压(mean pulmonary artery pressure, mPAP)升高的疾病。按照病因的不同,世界卫生组织(WHO)将其分为 5 类,包括动脉性 PH、左心疾病引起的 PH、缺氧或慢性肺部疾病引起的 PH、慢性血栓栓塞性 PH 和其他原因引起的 PH^[29]。PH 的特征是内皮功能障碍、肺动脉平滑肌细胞和成纤维细胞过度增殖而导致的肺小动脉闭塞和肺血管重塑^[30]。

除了血流动力学标准(在海平面、静息状态下,经右心导管检查测定的 mPAP \geq 25 mmHg)以外,在 PH 发生过程中的分子变化的共同点之一是线粒体功能障碍^[31]。同时,在各种 PH 中常见的血管重塑与线粒体功能紊乱有关^[32]。线粒体融合和裂变的

失衡影响PH的肺血管重构,以血管细胞过度增殖、抗凋亡表型为特征^[33]。肺血管平滑肌细胞(pulmonary artery smooth muscle cell, PASM)是线粒体导致PH表型变化的主要受体细胞。近期研究表明,PH患者PASM中Drp1表达显著升高,Ser616位点的磷酸化比例增加,促进PASM增殖;使用Mdivi-1后,PH患者的PASM增殖显著降低^[34]。而MFN2过表达导致线粒体融合途径过度激活时,则PASM增殖减少,细胞凋亡增加^[35]。同时有研究发现,通过抑制活化T细胞的核因子(nucleic factor of activated T-cell, NFAT)和缺氧诱导因子等转录因子的活性可以减少PASM的增殖,而抑制Survivin的表达可以增加PASM的凋亡,进而延缓PH疾病的进展^[36]。此外,Drp1通过阻断线粒体钙单向转运蛋白来减少线粒体Ca²⁺内流,促进肺动脉内皮细胞迁移、增殖,并抑制其凋亡,从而参与肺动脉新生血管形成,表明Drp1调控线粒体动力学在肺血管重塑中的新作用^[37]。除了肺动脉平滑肌细胞及内皮细胞外,Drp1还通过促进巨噬细胞介导的炎症反应诱导损伤的血管内膜增厚,巨噬细胞中的Drp1可能是血管疾病的潜在治疗靶点^[38]。

由此可见线粒体融合和裂变失衡是导致PH发生的重要因素,对其相关机制的研究也可以为临床治疗PH患者提供新的策略,但目前临床结果较少,治疗的有效性仍待验证,需要进一步的探索^[39]。

2.2 COPD

COPD是一种以持续气流受限和呼吸道症状为主要临床特征的慢性呼吸系统疾病,包括肺气肿、慢性支气管炎和小气道疾病3种病理表型^[40]。COPD的特点是肺功能进行性下降,导致发病率、入院率和病死率都比较高^[41]。同时,吸烟引起肺部炎症和氧化应激增加,是COPD的主要病理生理机制之一^[42]。深入探索COPD的发病机制,对于发现新的药物作用靶点和干预方案,具有重要的临床意义。

mtDNA中缺乏保护性组蛋白,因此在受到刺激时mtDNA更容易受到损伤,当mtDNA受损或耗尽时,线粒体融合和裂变失衡^[43]。体外实验表明,香烟烟雾对COPD模型中肺泡细胞的线粒体形态呈现多种影响。无毒剂量的香烟烟雾诱导小鼠肺泡细胞线粒体伸长,同时代谢活性增加,而无线粒体损伤^[44];暴露于高浓度的香烟烟雾可诱导肺泡细胞线粒体断裂,从而产生氧化应激影响线粒体功能^[45]。

COPD患者肺泡细胞的线粒体形态和动力学发生改变。在肺气肿患者中,肺泡2型细胞(alveolar

type II cell, AT II)的线粒体与正常人AT II相比,融合和裂变过程受损^[46]。研究发现,与不吸烟组COPD患者相比,吸烟组COPD患者通过上调生长抑素,增加过氧化物的生成,使AT II中介导线粒体分裂的Drp1中Ser616磷酸化水平显著升高,而调控线粒体融合的MFN1、MFN2、OPA1等相关分子表达下降,导致线粒体动力学异常。同时在吸烟组COPD患者中观察到线粒体形态异常,如线粒体肿胀、碎片化增加、线粒体嵴减少^[47]。在小鼠模型中,Drp1表达显著增加,线粒体异常分裂,肺泡上皮细胞(alveolar epithelial cell, AEC)凋亡。然而,使用Mdivi-1干预能降低小鼠AEC凋亡,同时能缓解香烟诱导的黏膜纤毛清除功能障碍,延缓肺气肿的进展。

研究发现,MitoTEMPO是一种线粒体靶向超氧化物歧化酶模拟物,可以减少香烟烟雾诱导的肺泡细胞的线粒体碎裂与细胞凋亡,在COPD的治疗中可能具备一定的价值。靶向干预线粒体融合分裂相关蛋白也可延缓COPD的进展^[48],如前文提到的Drp1抑制剂Mdivi-1,但临床疗效仍需进一步验证。因此,针对线粒体融合和裂变的深入研究,可以为COPD患者诊疗提供新的角度和方案^[49]。

2.3 急性肺损伤(acute lung injury, ALI)

ALI是以急性进行性呼吸衰竭为特征的一种常见且病死率高的临床综合征,严重时可进展为急性呼吸窘迫综合征(acute respiratory distress syndrome, ARDS),严重威胁患者生命并影响其生存质量^[50]。尽管在ALI和ARDS的药物干预和呼吸机管理方面取得了重大进展,但仍有40%的患者最终死亡^[51]。ALI的特点是AEC凋亡^[52]和肺泡上皮屏障破坏^[53],导致肺泡内液体积聚、肺泡表面活性降低和肺血气交换功能受影响^[54]。

在ALI小鼠模型中,小鼠体内Drp1的磷酸化位点被激活,诱导线粒体裂变^[55],表现为线粒体的碎片化和膜去极化,促进细胞色素c凋亡蛋白从线粒体转移到细胞质^[56],细胞质中细胞色素c会诱导Caspase-3激活,导致细胞凋亡^[57]。AEC之间的紧密连接分子由封闭蛋白和封闭小带组成,并且在维持肺泡上皮屏障方面发挥着关键作用^[58]。近期研究发现线粒体Drp1易位和Caspase-3激活降低封闭蛋白和封闭小带的表达^[59],破坏肺泡上皮屏障,加速ALI的进展。但加入Mdivi-1后可以抑制Drp1易位和Caspase-3活化,这也证实了Drp1介导的线粒体裂变在ALI中的作用,在ALI个体的AEC中调节Drp1介导的线粒体裂变可能是ALI的潜在治疗方法。

MitoQ是一种脂溶性小分子,是最具代表性的靶向线粒体的抗氧化剂^[60]。MitoQ的保护作用很大程度上取决于核因子E2相关因子2(nuclear factor E2 related factor 2, Nrf2)的激活^[61],并通过促进多种细胞保护酶的表达来维持细胞正常功能。研究表明MitoQ通过激活Nrf2途径调节Drp1介导的线粒体裂变来减轻小鼠模型中的ALI^[62],使用Mdivi-1可以抑制ALI中Nrf2和Drp1激活起到保护肺泡上皮屏障的作用^[63],ALI的治疗有望从线粒体的融合和裂变中找到新的策略。

2.4 特发性肺纤维化(idiopathic pulmonary fibrosis, IPF)

IPF是最难治疗的呼吸系统疾病之一,发病率逐年上升,主要发生在50岁以上的中老年人^[64]。该病早期表现不明显,明确诊断后预后极差。IPF患者发生PH、肺癌和心血管疾病的概率很高,这大大增加了临床治疗的困难^[65]。在IPF的临床研究中,研究人员发现细胞出现端粒磨损和氧化应激等衰老的特征,证实了肺纤维化与细胞衰老有显著联系^[66]。由此可见,细胞衰老在一定程度上促进了肺纤维化的发生,研究细胞衰老的相关机制有助于探索IPF的治疗方法。

线粒体的融合和裂变在多种细胞衰老机制中发挥着重要作用。在衰老细胞中,可以观察到线粒体的变化,包括mtDNA突变导致的大小增加、线粒体嵴缺失等形态学变化^[67]。这些改变会损害线粒体活性,研究人员最近在IPF患者肺部的巨噬细胞、AEC和成纤维细胞中检测到线粒体功能障碍,如在AT II细胞损伤与纤维化重塑中发现MFN1/2的异常表达^[68]。

AEC是IPF发病过程中重要的靶细胞,研究人员发现IPF中AEC线粒体增大,单细胞测序也提示IPF中MFN2的mRNA表达升高。此外,在动物模型中发现小鼠AT II中的Drp1失活,而MFN1和MFN2的缺失会导致自发性肺纤维化,表明线粒体融合在IPF的AEC中占主导地位^[69]。

这些发现强调了MFN1/2在IPF中的重要性。IPF还与复杂的线粒体形态异常有关,包括线粒体的融合和断裂,以及线粒体嵴的改变^[70],而OPA1是介导线粒体嵴融合的关键分子,在IPF中的研究较少,值得进行深入研究。

2.5 新型冠状病毒肺炎

新型冠状病毒肺炎(简称新冠肺炎)是一种由新型严重急性呼吸综合征 β 冠状病毒(severe acute

respiratory syndrome coronavirus 2, SARS-CoV-2)引起的急性呼吸道疾病,该病毒是一种包膜的单链RNA病毒^[71]。病毒感染后,约5%的患者出现呼吸衰竭,需要住院治疗^[72]。SARS-CoV-2通过破坏AEC和PASMC的线粒体,引发细胞凋亡和生物能量损伤,最终造成肺泡损伤和低氧血症^[73]。

线粒体在新冠肺炎的致病过程中起着重要作用^[71]。病毒通过模拟宿主细胞中凋亡蛋白的同源物转录或通过宿主细胞中调控凋亡的蛋白相互作用来诱导细胞凋亡^[74]。研究发现,SARS-CoV-2可以打开线粒体通透性转换孔(mitochondrial permeability transition pore, mPTP)^[75],诱导线粒体膜去极化。mPTP开放和线粒体膜去极化导致促细胞凋亡蛋白结构域受损,使OMM通透性增加,线粒体膜间隙释放凋亡诱导因子(apoptosis-inducing factor, AIF)和细胞色素c^[76]。释放的AIF和细胞色素c激活Caspase-3并进入细胞核,促进DNA降解,导致细胞凋亡^[77]。研究表明SARS-CoV-2影响参与线粒体电子传递和细胞凋亡相关蛋白的表达^[78]。通过转录组学鉴定,发现SARS-CoV-2感染上调了线粒体中总Drp1的表达,激活了Drp1 Ser616的磷酸化,增加了线粒体裂变。体外实验也表明SARS-CoV-2在AEC中引起了显著的线粒体分裂,是新冠肺炎的一个重要标志^[79]。

3 线粒体融合和裂变在呼吸系统疾病中的临床应用价值

探讨呼吸系统疾病发生发展机制是寻找临床精准分子治疗靶点的重要方式,线粒体融合和裂变是呼吸系统相关疾病临床治疗的潜在靶点。许多药物靶向线粒体的融合和裂变途径,维持线粒体融合和裂变的动态平衡。

罗氟司特可以用于治疗伴支气管炎的重症COPD患者^[80]。研究表明,罗氟司特通过抑制AEC中Drp1的Ser616位点磷酸化来减少香烟烟雾诱导的细胞死亡。可见,罗氟司特通过抑制线粒体分裂而对AEC具有保护作用^[81]。曲美他嗪通过调节线粒体融合和裂变改善肺血管重构从而治疗PH。研究表明,低剂量曲美他嗪通过提高新生儿心肌细胞中融合线粒体的比例来增加线粒体功能^[82]。缺氧条件下使用曲美他嗪可以恢复PASMC的 $\Delta\Psi_m$,并通过依赖Drp1的机制阻止缺氧诱导的PASMC增殖^[83]。同时,曲前列尼尔(前列环素模拟物)招募前列环素受体或前列腺素E2受体激活腺苷环化酶,提

高细胞内 cAMP 水平进而激活蛋白激酶 A^[84], 诱导 Drp1 在 Ser637 处的抑制性磷酸化, 并抑制 Drp1 在 Ser616 处的刺激性磷酸化, 减少线粒体裂变, 抑制 PH 过程中 PSMC 增殖的作用^[85]。

越来越多的研究表明许多天然化合物对线粒体融合和裂变具有潜在效应。如黄芩素在急性肺损伤中通过抑制 Drp1 在 Ser616 处的磷酸化来减少线粒体裂变^[86], 柑橘皮中的多甲氧基黄酮可降低 COPD 患者 AEC 中 Drp1 的蛋白表达水平^[87]。因此, 对天然化合物的疗效评估, 可能成为线粒体裂变相关损伤的临床诊疗新方向^[88]。

4 小结与展望

随着年龄的增加以及环境刺激因素的影响, 细胞中线粒体动力学的平衡紊乱, 导致线粒体过度融合或裂变, 诱发多种呼吸系统疾病的发生发展。因此, 进行线粒体融合和裂变相关研究, 围绕线粒体动力学进行相关肺疾病的干预和药物研发成为当前的研究热点。调控线粒体动力学的平衡是肺部疾病治疗干预的有效方式, 线粒体相关靶蛋白 MFN1/2、OPA1、Drp1 等及其相关信号通路如 Nrf2 已被证明在呼吸系统相关疾病中起着重要作用。在此基础上, 深入开展线粒体的融合和分裂在呼吸系统相关疾病中的发病机制以及药物靶向位点的研究, 有望为临床精准诊疗呼吸系统相关疾病提供新的方案。

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