·综述·

线粒体质量控制在脓毒症急性肺损伤中的作用

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【摘 要】 脓毒症诱导的急性肺损伤(ALI)临床常见,发病率和死亡率高。线粒体质量控制在脓毒症ALI中发挥着至关重要的作用,其过程包括线粒体生物合成、线粒体融合与分裂和线粒体自噬等。线粒体质量控制失调会引起线粒体功能障碍,从而诱发肺内皮细胞程序性死亡,是ALI发生的重要机制。因此,当前很多研究关注线粒体质量控制的作用,并将其作为脓毒症ALI的靶向治疗策略。本文就线粒体质量控制在脓毒症ALI的相关研究进展展开综述,为临床防治脓毒症ALI提供理论参考依据。

【关键词】 脓毒症;急性肺损伤;线粒体质量控制
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Role of mitochondrial quality control in sepsis-induced acute lung injury

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【Abstract】 Sepsis induced acute lung injury (ALI) is common clinically, with high incidence rate and mortality. Mitochondrial quality control plays a crucial role in sepsis induced ALI, including mitochondrial biosynthesis, mitochondrial fusion and fission, and mitophagy. Impairment of mitochondrial quality control can lead to mitochondrial dysfunction, leading to programmed death of pulmonary endothelial cells, which is an important mechanism for pathogenesis of ALI. Therefore, in recent years many studies have focused on the mitochondrial quality control as a targeted treatment strategy for sepsis induced ALI. In this study, we reviewed the recent research progress of mitochondrial quality control in septic induced ALI, hoping to provide theoretical reference for the clinical prevention and treatment of septic induced ALI.

【Key words】 sepsis; acute lung injury; mitochondrial quality control
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脓毒症是由感染因素引起的全身炎症反应综合征,是临床上常见的一种并发症[1]。了解脓毒症中急性肺损伤(acute lung injury, ALI)的发生机制对治疗脓毒症ALI患者具有重要意义。在脓毒症的影响下,免疫细胞、骨骼肌细胞和肺内皮细胞均有关于线粒体超微结构损伤和线粒体功能障碍的相关报道[2,3]。同时,在脓毒症患者和脓毒症实验模型中都观察到腺苷三磷酸(adenosine triphosphate, ATP)耗竭、细胞内抗氧化系统受损和呼吸链受到抑制等现象[4]。持续性线粒体功能障碍可导致相关的器官衰竭和患者的预后不良。因此,功能障碍线粒体的清除和健康线粒体的产生对促进脓毒症中相关器官的功能恢复具有重要意义。本文主要阐明了线粒体质量控制的具体分子机制和线粒体质量控制体系紊乱在脓毒症ALI中的发病机制,期待为后续特异性治疗提供新策略。

1 线粒体质量控制体系

1.1 线粒体生成

线粒体生成是由细胞核基因和线粒体基因共同调控的。在线粒体生成过程中最主要的调节基因是过氧化物酶增值物激活受体共激活物1α基因(*peroxisome proliferator-activated receptor gamma coactivator 1 alpha*, *PGC*-1α),其表达受到多种因素影响[5]。*PGC*-1α下游的调控机制是通过激活两个关键的转录因子,即核呼吸因子(nuclear respiratory factor, NRF)1,2。*PGC*-1α与NRF1,2相互作用,激活线粒体转录因子A(mitochondrial transcription

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factor A, TFAM),然后结合到线粒体电子传递链中 5 个复合物亚基的启动子区域,启动线粒体脱氧核糖核酸(mitochondrial deoxyribonucleic acid, mtDNA)的复制和转录,从而使线粒体数量增加[6]。

1.2 线粒体融合与分裂

相较于线粒体生成而言,线粒体的融合与分裂机制相对更加复杂。哺乳动物线粒体融合是在线粒体融合蛋白 1(mitofusin 1, Mfn 1)、融合蛋白 2(mitofusin 2, Mfn 2)和视神经萎缩蛋白 1(optic atrophy 1, OPA1)共同介导下完成的。Mfn1 和 Mfn2 负责线粒体外膜的融合,而 OPA1 负责线粒体内膜的融合[7]。哺乳动物线粒体裂变是由动力相关蛋白 1(dynamin-related protein 1, Drp1)、线粒体裂变蛋白 1(adaptor fission 1, Fis1)、线粒体动力蛋白 49 ku(mitochondrial dynamics proteins of 49 ku, MID49)、线粒体动力蛋白 51 ku(mitochondrial dynamics proteins of 51 ku, MID51)共同介导的。Drp1 是一种细胞质蛋白,可以通过与线粒体裂殖因子(mitochondrial fission factor, Mff)、Fis1、MID49、MID51 结合来促进线粒体分裂为两个独立的细胞器[8]。其中,Drp1 从细胞质转移到线粒体是线粒体分裂的关键。Drp1 缺失将使线粒体呈过度融合状,而 Drp1 活化将在靶点部位形成螺旋式多聚物,在内质网和肌动蛋白丝协同作用下,将线粒体一分为二[9]。总之,通过影响 Drp1 的活化可以改变线粒体融合与分裂过程,进而改变线粒体的分布、质量和稳定度。

1.3 线粒体自噬

线粒体自噬是将线粒体在溶酶体内进行降解,在线粒体质量控制中具有重要作用。目前已知的线粒体自噬有两种机制:一种是由磷酸化肿瘤抑制蛋白-帕金森蛋白(phosphatase and tension homolog-induced putative kinase1-Parkin, PINK1-Parkin)介导的线粒体自噬,另一种是由受体直接介导的线粒体自噬[10]。Parkin 是一种位于细胞质内的 E3 泛素化连接酶,PINK1 是一种位于线粒体上的丝氨酸/苏氨酸激酶。正常情况下,PINK1 会被早老素相关菱形样蛋白(presenilin associated rhomboid like protein, PARL)处理并降解。而线粒体外膜蛋白 7(translocase of outer mitochondrial membrane 7, TOMM7)可使 PINK1 蛋白免受降解[11]。线粒体受到应激发生去膜电位后,PINK1 在丝氨酸位点发生磷酸化,以电压依赖的方式聚集在线粒体上,招集 Parkin 并使其磷酸化,促进隔离蛋白 1(sequestosome-1, p62)的表达并与损伤的线粒体结合。损伤的线粒体随后与轻链 3(light chain 3, LC3)结合,被溶酶体降解。PINK1 可募集细胞质中 Parkin 到线粒体从而启动 PINK1-Parkin 介导的线粒体自噬通路[12]。另一种由受体直接介导的自噬是依赖于受体自身含有的跨膜结构域,直接结合 LC3,诱导线粒体自噬的发生(图 1)[13]。

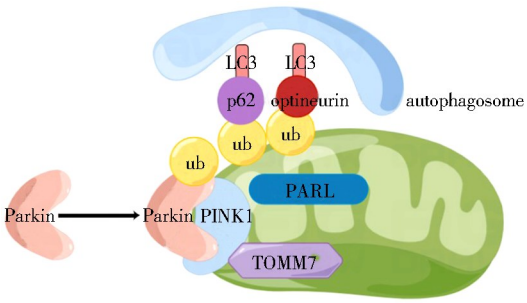

图 1 PINK1-Parkin 介导的自噬通路

Figure 1 PINK1-Parkin mediated autophagy pathway

PINK1: phosphatase and tension homolog-induced putative kinase 1; TOMM7: translocase of outer mitochondrial membrane 7; PARL: presenilin associated rhomboid like protein; LC3: light chain 3; p62: sequestosome-1; ub: ubiquitin.

2 线粒体质量控制体系与脓毒症 ALI 的关系

2.1 线粒体生成与脓毒症 ALI 的关系

损伤相关分子模式(damage-associated molecular pattern, DAMP)是存在于细胞核、细胞质和线粒体中的总多内源性风险因子的总称,它们在细胞死亡或应激时被释放[14]。在脓毒症诱导的 ALI 中,作为线粒体内的 DAMPs,mtDNA 主要通过两种方式增加肺内皮细胞的通透性,从而进一步加重 ALI[15]。第一种是通过激活核苷酸结合寡聚体样受体家族含有 Pyrin 结构域的蛋白质 3(nucleotide-binding oligomerization domain-like receptor family pyrin domain contain 3, NLRP3)并与之相互作用加重炎症反应;第二种是通过激活 toll 样受体 9(toll-like receptor 9, TLR-9)触发免疫反应加重肺损伤[16]。Zeng 等[17]证明过多的 mtDNA 可通过激活 TLR-9 触发先天性免疫反应,从而加重脓毒症所导致 ALI。然而,有相关研究却指出,增加 *PGC*-1α 基因的表达可以提高脓毒症 ALI 患者的生存率,而抑制表达则会使预后恶化[18]。这是因为新生成的线粒体可以替代受损的线粒体,使线粒体功能尽早的恢复,从而起到保护肺组织的作用。这两项研究之所以会得到相反的结果,可能是因为刺激线粒体生物合成过度,扰乱了基因转录的复杂过程或线粒体融合与分裂过程,导致线粒体功能受损。虽然线粒体合成是线粒体功能损伤的代偿机制,但过度地触发也会导致线粒体功能损伤。或者说,单纯依赖线粒体生物合成不足以代偿脓毒症 ALI 情况下线粒体功能的受损。

2.2 线粒体融合(分裂)与脓毒症 ALI 的关系

线粒体融合与分裂分别由融合相关蛋白 Mfn1、Mfn2、OPA1 和分裂相关蛋白 Drp1 介导。凡是能够影响四种蛋白合成的过程均可改变线粒体融合与分

裂的平衡。在目前的研究中,血红素氧合酶/一氧化碳系统(heme oxygenase-1/carbon monoxide system, HO-1)已经被证明可通过调节线粒体融合与分裂过程来缓解由内毒素引起的脓毒症 ALI[19]。在脂多糖(lipopolysaccharide, LPS)诱导下的脓毒症 ALI 大鼠模型中,Mfn-1 的表达受到 HO-1 抑制,从而降低线粒体融合,改善氧化应激状态[20]。线粒体分裂抑制剂能够缓解 LPS 诱导的丝裂原活化蛋白激酶(mitogen-activated protein kinases, MAPKs)的激活,减少促炎因子的释放,从而抑制线粒体分裂,减轻 ALI 的损伤程度[21]。在脓毒症 ALI 小鼠模型中,可以通过抑制 Drp1 诱导的线粒体分裂来减轻肺损伤的程度[22]。然而,下调融合基因表达对改善线粒体功能并不是必然结果。Zhang 等[23]发现在脓毒症 ALI 小鼠模型中 Mfn-2 表达下降,Drp-1 表达升高,线粒体融合降低,分裂增加,导致线粒体网络中断,加重肺组织损伤。同样,Ning 等[24]发现通过抑制线粒体分裂,增强线粒体融合可以起到保护肺组织的作用。在另一个脓毒症 ALI 体外模型中发现:脓毒症可以促进髓系细胞上激发受体 1(triggering receptor expressed on myeloid cells 1, Trem-1)的表达,从而增加 Mfn-2 在巨噬细胞中的特异性表达,起到保护肺组织的作用[25]。两个实验在线粒体融合相关蛋白 Mfn-2 表达上出现相反的结果可能是因为两种模型造成的肺损伤程度不同,Zhang 等[23]处理的模型尚存在其他保护机制,如线粒体自噬。因此,线粒体的生物融合与分裂在脓毒症 ALI 疾病发展过程中的作用仍待进一步商榷。

2.3 线粒体自噬与脓毒症 ALI 的关系

脓毒症 ALI 肺功能的恢复依赖于清除受损的线粒体以及良好线粒体的再生[26]。正常的线粒体自噬通过切割和降解受损的线粒体来维持细胞的稳态,而过度的线粒体自噬则可能会导致线粒体功能障碍从而造成细胞损伤和死亡。转录因子 EB(transcription factor EB, TFEB)通过负向调节线粒体自噬并减轻线粒体损伤从而保护肺组织[27]。*PGC*-1α 基因的表达可正向调控 TFEB 的表达,进而减弱线粒体自噬,缓解肺水肿,减轻炎症[28]。Zhao 等[29]证实,通过抑制 Parkin1 从细胞质到线粒体的翻译以及 Parkin 介导的线粒体自噬可以缓解由 LPS 诱导的 ALI。此外,B 细胞淋巴瘤 2(B-cell lymphoma 2, Bcl-2)蛋白的过表达也可减弱线粒体自噬从而起到保护肺组织的作用[23]。然而,有相关研究却指出,通过诱导 PINK1 的表达,促进 Parkin 的易位,启动线粒体自噬可以起到对肺组织的保护作用[30]。所以目前仍无法确定在脓毒症中,自噬的主要功能是清除受损线粒体,还是参与细胞程序性凋亡的某个方面。需要进一步的研究来验证在脓毒症相关的 ALI 中自噬对于线粒体的作用和调节机制。

3 以线粒体质量控制为靶点的脓毒症 ALI 干预策略

恢复线粒体质量控制的干预措施可能是治疗脓毒症 ALI 的策略,如苏黄止咳胶囊可抑制炎症小体的激活,减弱炎症细胞浸润,维持线粒体稳态,减轻 ALI[31]。氢气可增强 PINK1 的活性并降低细胞凋亡标志物的表达,是治疗脓毒症 ALI 的潜在药物[32]。同时,LC3 蛋白的过表达也能够增强线粒体自噬,提高肺组织的生存率,减轻炎症细胞的浸润[33]。此外,药物还可通过影响线粒体的融合与分裂过程从而减轻脓毒症造成的 ALI。右美托咪定可通过降低肺组织中线粒体融合蛋白 OPA1、Mfn1、Mfn2 的表达从而起到保护肺组织的作用[34]。帕罗西林也被证明可通过影响线粒体分裂减轻脓毒症 ALI[35]。综上,针对线粒体质量控制的药物以线粒体合成、融合与分裂和自噬为目标,恢复线粒体功能,最终预防脓毒症 ALI 的发生(表 1)。

综上,线粒体质量控制分子机制研究进展迅速,相关基因通路也已被阐明,然而对于脓毒症 ALI 中如何调控线粒体质量的潜在机制仍不清楚。探讨线粒体质量控制有效的调控机制,有利于寻求线粒体靶向治疗策略,为临床防止脓毒症 ALI 提供思路和理论依据,对脓毒症 ALI 患者的治疗具有重要的临床意义。

表 1 线粒体质量控制治疗脓毒症 ALI 现有靶点

Table 1 Current potential targets for mitochondrial quality control in sepsis ALI

Mitochondrial quality control	Drug	Targets	Reference
Mitochondrial fusion(-)	Dexmedetomidine	Inhibition of OPA1, Mfn1, Mfn2	[34]
Mitochondrial division(-)	Suhuang antitussive capsule	Promotion of Drp1	[31]
Mitochondrial division(-)	Paroxicillin	Inhibition Of Drp1	[35]
Mitochondrial division(-)	Melatonin	Inhibition Of Drp1	[24]
Mitochondrial autophagy (+)	Hydrogen	Promotion of PINK1	[32]

(+): promotion; (-): inhibition; ALI: acute lung injury; PINK1: phosphatase and tension homolog-induced putative kinase1; OPA 1: optic atrophy 1; Mfn1: mitofusin 1; Mfn2: mitofusin 2; NLRP3: nucleotide-binding oligomerization domain-like receptor family pyrin domain contain 3; Drp 1: dynamin-related protein 1.

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