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·综述·

牙周致病菌诱导线粒体功能障碍促进牙周炎的研究进展

李丽敏[1]，　彭显[2]，　周学东[1]

1.口腔疾病防治全国重点实验室 国家口腔医学中心 国家口腔疾病临床医学研究中心 四川大学华西口腔医院牙体牙髓病科，四川 成都(610041)；　2.口腔疾病防治全国重点实验室 国家口腔医学中心 国家口腔疾病临床医学研究中心 四川大学华西口腔医院，四川 成都(610041)

【摘要】 线粒体是广泛存在于真核细胞中的能量代谢细胞器，细菌感染宿主后能干扰线粒体正常功能，引发线粒体功能障碍。线粒体功能障碍与多种炎症性疾病密切相关，牙周炎是由病原微生物感染引起的牙周组织慢性炎症性疾病，近年研究发现，线粒体功能障碍可能在该病的发生发展中起关键作用。与健康牙周组织相比，炎性牙周组织表现出更显著的线粒体功能障碍，而该病理过程与牙周致病菌的感染密切相关。研究表明，牙周致病菌可通过多种途径干扰宿主牙龈上皮细胞、牙龈成纤维细胞等细胞的线粒体稳态，包括：诱导线粒体生物发生紊乱；干扰线粒体动力学，促进线粒体分裂；抑制线粒体自噬；影响线粒体功能障碍相关细胞凋亡以及诱导内源性氧化应激，上调炎症因子的表达，从而促进炎症微环境的形成和持续。本文综述牙周致病菌对线粒体生物学功能的影响及其在牙周炎进展中的作用机制，以期为开发靶向线粒体的牙周炎治疗策略提供新思路。

【关键词】 线粒体；　牙周炎；　牙周致病菌；　线粒体功能障碍；　线粒体生物发生；　线粒体动力学；　线粒体自噬

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Research progress on periodontal pathogen inducing mitochondrial dysfunction promoting periodontitis

LI Limin[1], PENG Xian[2], ZHOU Xuedong[1].　1. State Key Laboratory of Oral Diseases & National Center for Stomatology & National Clinical Research Center for Oral Diseases & Department of Operative Dentistry and Endodontics, West China Hospital of Stomatology, Sichuan University, Chengdu 610041, China;　2. State Key Laboratory of Oral Diseases & National Center for Stomatology & National Clinical Research Center for Oral Dis-eases & West China Hospital of Stomatology, Sichuan University, Chengdu 610041, China

Corresponding author: ZHOU Xuedong, Email: zhouxd@scu.edu.cn

【Abstract】 Mitochondria, ubiquitous energy-producing organelles in eukaryotic cells, can have their normal functions disrupted by bacterial infections, leading to mitochondrial dysfunction. This dysfunction is closely associated with inflammatory diseases. Periodontitis, a chronic inflammatory disorder of periodontal tissues caused by pathogenic microorganisms, has been increasingly linked to mitochondrial dysfunction in its pathogenesis and progression. Compared to healthy periodontal tissues, inflammatory lesions exhibit more pronounced mitochondrial dysfunction—a pathological process that is strongly correlated with periodontal pathogen infection. Studies reveal that these pathogens disrupt mitochondrial homeostasis in host cells (e.g., gingival epithelial cells and fibroblasts) through multiple mechanisms, including disrupting mitochondrial biogenesis, altering mitochondrial dynamics (promoting excessive fission), inhibiting mi-

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【作者简介】李丽敏，硕士，Email：lilimin@stu.scu.edu.cn

【通信作者】周学东，教授，博士，Email：zhouxd@scu.edu.cn

tophagy, impairing mitochondrial dysfunction-associated apoptosis, and inducing endogenous oxidative stress, which up-regulates pro-inflammatory cytokines. Collectively, these processes drive the establishment and persistence of an inflammatory microenvironment. This review explores how periodontal pathogens affect mitochondrial function and their mechanistic contributions to periodontitis progression, with the goal of providing novel insights for developing mitochondria-targeted therapeutic strategies.

【Key words】 mitochondria; periodontitis; periodontal pathogen; mitochondrial dysfunction; mitochondrial biogenesis; mitochondrial dynamics; mitophagy

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线粒体是广泛存在于真核细胞中的能量代谢细胞器，为多种生命活动供能[1]。为了维持其功能稳态，线粒体形成了高度动态的质量控制机制，包括线粒体生物发生、动力学和自噬等过程[2]。这一稳态一旦失衡，可能导致线粒体功能障碍，并促进炎症反应。例如，在线粒体能量代谢过程中产生的大量活性氧（reactive oxygen species，ROS）可造成线粒体DNA（mitochondrial DNA，mtDNA）损伤或外排，从而引发炎症[3-4]。

研究显示，线粒体功能障碍与多种炎症性疾病密切相关，广泛涉及心血管、神经和消化系统等多个领域[5-7]。牙周炎是由微生物感染引起的一种慢性炎症性疾病，未及时控制将引起牙齿松动和缺失[8-9]。牙周炎病灶中存在特异性牙周致病菌，如牙龈卟啉单胞菌（*Porphyromonas gingivalis*，*P.g*）、伴放线聚集杆菌（*Aggregatibacteractinomycetemcomitans*，*A.a*）、具核梭杆菌（*Fusobacterium nucleatum*，*F.n*）等[10-11]，这些病原微生物可以损伤牙周组织，诱导牙周炎症[12-13]。近年研究发现，牙周致病菌感染可诱导牙周组织发生线粒体功能障碍，这可能在牙周炎发病机制中有重要意义。与健康牙周组织相比，研究者们在炎性牙周组织中观察到更显著的线粒体结构异常及功能障碍[14-15]。其中，*P.g*的脂多糖可诱导人牙龈成纤维细胞（human gingival fibroblasts，HGFs）出现线粒体功能障碍[14]。而*F.n*感染可上调牙龈上皮细胞中线粒体ROS的水平，此效应可受定位于线粒体的NOD样受体NLRX1（NOD-like receptor family member X1，NLRX1）的正反馈调节[16]。

笔者将从线粒体生物发生、线粒体动力学、线粒体自噬、线粒体功能障碍相关细胞凋亡以及内源性氧化应激等方面综述牙周致病菌对线粒体生物学功能的影响及其在牙周炎进展中的作用机制，为探索靶向线粒体的牙周病新型治疗策略提供思路。

1　牙周致病菌诱导线粒体生物发生紊乱

线粒体生物发生是一个受核基因和线粒体基因协调精密调控的过程[17]，该程序的正确运行有助于维护mtDNA稳态，调整线粒体的尺寸与数量，使线粒体功能状态保持稳定与平衡[18]。mtDNA与线粒体功能密切相关[19]，其稳态异常，包括mtDNA的损伤、拷贝数变化以及外排[20]，都可能导致线粒体功能障碍[21-22]，进而引发炎症[23-24]。

许多研究表明，炎性牙周组织中存在线粒体功能障碍[25-29]。与健康个体相比，来自慢性牙周炎患者的人牙龈成纤维细胞中可检测到更显著的线粒体结构破坏、ROS水平升高以及mtDNA水平下降[30-31]。在脂多糖诱导的牙周炎模型中，牙周组织细胞中也被观察到线粒体功能障碍[14,32-33]。*P.g*脂多糖可诱导人牙龈成纤维细胞线粒体生物发生紊乱以及mtDNA拷贝数减少，引起线粒体数量下降，并且导致人牙龈成纤维细胞中磷酸化过氧化物酶体增殖物激活受体γ共激活因子1α（peroxisome proliferator activated receptor γ coactivator-1α，PGC-1α）和线粒体转录因子A（mitochondrial transcription factor A，TFAM）水平下降，伴线粒体耗氧率和磷酸腺苷（adenosine triphosphate，ATP）水平下降[14,34-35]。此外，*P.g*脂多糖可以作用于人牙龈成纤维细胞，上调ROS水平并导致线粒体通透性转变孔（mitochondrial permeability transition pore，mPTP）开放，从而引起mtDNA释放，这种mtDNA的外排和相应炎症途径的激活可能与牙周炎症的扩散相关[22,36]。

还有研究表明，*F.n*感染牙龈上皮细胞后能破坏线粒体膜电位，引起线粒体ROS累积，诱导mtDNA外排，这可能与牙周炎的促进或维持有关[16]。

横断面研究表明，牙周炎患者血浆无细胞线粒体DNA（cell-free mito-chondrial DNA，cf-mtDNA）水平与探诊深度、附着水平以及出血指数等牙周炎临床指标之间呈正相关，此外，牙周炎组的cf-mtDNA水平显著高于健康组[37]，而这可能与牙周致病菌诱导的mtDNA外泄相关。

2　牙周致病菌干扰线粒体动力学，促进线粒体分裂

线粒体是高度动态的细胞器，在不同的细胞能量需求、代谢状态条件下，通过动态的融合和裂变事件，产生特定复杂的管状结构网络，即线粒体形态网络[38]。线粒体融合与裂变在动态中保持平衡状态，即为线粒体动力学。这一动态平衡的维持对于线粒体形态网络适应细胞和外部信号的需要具有重要意义。

在哺乳动物细胞中，线粒体的融合由丝裂蛋白1、丝裂蛋白2以及视神经萎缩蛋白1的调控，而线粒体的分裂主要由膜内寡聚的动力相关蛋白1（dynamin-related protein 1，DRP1）进行[39]。有研究者发现，线粒体动力学的失衡可能引起细胞代谢重编程[40]，干扰细胞呼吸[41]，影响ROS水平[42]。此外，线粒体动力学的扰动可能导致mtDNA的异位，后者可作为线粒体损伤相关分子模式，通过激活cGAS-STING通路激活Ⅰ型干扰素反应进而诱导炎症[43]。

*P.g*能够通过刺激DRP1依赖的线粒体裂变破坏线粒体能量合成，并且诱导炎症。研究发现，Pg脂多糖能诱导人牙龈成纤维细胞中线粒体数量增加以及ATP水平降低[44]，而敲低DRP1可以逆转人牙龈成纤维细胞中脂多糖感染引起的线粒体断裂、复合物Ⅰ活性降低以及ATP水平降低[45]，其中*P.g*诱导的ATP水平降低可能与其诱导的线粒体膜电位下降有关[46]。同样，*P.g*对线粒体分裂的促进作用在血管内皮细胞中也得到证实[47-48]。

此外，*P.g*能诱导炎症牙周组织中巨噬细胞的DRP1过度激活，进而发生线粒体裂变增加、线粒体膜电位受损以及线粒体ROS增加，诱导mPTP开放以及NLRP3炎性小体的激活[49]。目前，仍需要更多的研究来明确牙周致病菌及其各种毒力因子对牙周细胞线粒体动力学相关蛋白的影响。

3　牙周致病菌抑制线粒体自噬

线粒体自噬是线粒体的特异性自我清除，旨在清除缺陷或多余线粒体以维持线粒体质量，进而维护细胞正常功能[50]。

在该过程中，线粒体通过自噬相关蛋白32（autophagy-related protein 32，Atg32）、PTEN诱导假定激酶1-帕金蛋白（PTEN-induced putative kinase 1-Parkin RBR E3 ubiquitin-protein ligase，PINK1-Parkin）或线粒体自噬受体蛋白NIX通路，被自噬体吞噬，随后与溶酶体融合后降解，这一功能的抑制或者增强，均有可能致使细胞出现功能障碍，严重时甚至会诱发细胞死亡[51-53]。

研究表明，线粒体自噬功能障碍与牙周炎进展相关。在牙周炎患者的牙周韧带干细胞中，泛素C末端水解酶L1（ubiquitin C-terminal hydrolase L1，UCH-L1）表达上调，该酶通过负调控线粒体自噬依赖的骨形态发生蛋白2/Smad信号通路抑制牙周韧带干细胞的成骨分化，导致牙周组织修复能力受损，并可能促进牙周炎性环境的持续存在[54]。

在*P.g*感染的炎症牙龈组织中，Parkin与PINK1的mRNA及蛋白表达均有显著下降[55]，表明牙周炎症状态下牙周组织中线粒体自噬机制受损。还有研究发现，尽管*P.g*上调了口腔上皮细胞中PINK1-Parkin的表达，但也引起细胞内溶酶体缺失，并且显著减少PINK1标记的线粒体和溶酶体的共定位，提示*P.g*可能通过作用于溶酶体来抑制功能失调线粒体的自噬降解，造成功能障碍线粒体的堆积[56]。

4　牙周致病菌影响线粒体功能障碍相关细胞凋亡

细胞凋亡是在细胞内、外信号刺激下，通过死亡受体和线粒体介导途径启动的细胞程序性死亡[57-58]。当细胞遭受诸如DNA损伤、氧化应激等不良刺激时，B细胞淋巴瘤-2蛋白（B-cell lymphoma 2，Bcl-2）家族中发挥促凋亡作用的蛋白（主要是Bax和Bak）会被激活[59]。这些激活的蛋白会诱导线粒体发生一系列变化，包括线粒体内跨膜电位（mitochondrial inner membrane potential，MMP）的瓦解，以及线粒体的外膜通透性（mitochondrial outer membrane permeabilization，MOMP）增加，导致线粒体能量代谢紊乱以及线粒体促凋亡效应物的外溢，从而引起线粒体介导的细胞凋亡，即线粒体凋亡[60]。

一方面，牙周致病菌可能通过抑制线粒体功能障碍相关细胞凋亡维持炎症环境。在*P.g*感染早期的人上皮细胞中，牙龈蛋白酶粘附肽A44易位至线粒体，促使BCL-2的表达显著上调，同时抑制半胱天冬酶-9（caspase-9）的活性，抑制宿主细胞线粒体凋亡[61]。此外，*P.g*可以通过阻断效应子半胱天冬酶-3（caspase-3）的激活来抑制人牙龈细胞（human gingival cell，HGC）的凋亡[62]。学者们在牙龈上皮细胞中也观察到类似现象。*P.g*通过激活Jak/Stat/Akt通路，阻断caspase-3的活化，从而来抑制牙龈上皮细胞中的线粒体凋亡[35]。研究表明，*P.g*还能通过激活PI3K/Akt通路促进促凋亡蛋白Bad在Ser136位点发生磷酸化而灭活，进而抑制线粒体介导的牙龈上皮细胞凋亡[63]。然而，还有研究结果显示，尽管*P.g*感染能抑制牙龈上皮细胞的凋亡，但是在此期间，牙龈上皮细胞中PI3K/Akt信号转导减少，并且在抑制PI3K后，Bad在Ser136位点的磷酸化率显著下降[64]。

另一方面，牙周致病菌可能通过上调线粒体功能障碍相关细胞凋亡实现免疫抑制或逃逸。有研究发现，*P.g*能诱导巨噬细胞中mtDNA外排以及小鼠牙周炎模型中牙周组织的细胞凋亡和坏死增加，这可能有利于牙周致病菌诱导牙周炎症环境中的免疫抑制[65]。此外，*P.g*通过凋亡诱导因子（apoptosis-inducing factor，AIF）释放途径诱导上皮细胞的线粒体凋亡[66]，促进口腔组织损伤。*A.a*能诱导人B淋巴细胞系的线粒体功能障碍相关细胞凋亡[67-68]。

然而，细胞凋亡过程涉及多种信号通路和调控因子，某些抗凋亡因子的上调或下调不能等同于细胞凋亡受到促进或抑制。炎性牙周组织中是否存在线粒体调控的细胞凋亡机制仍需进一步探究。

5　牙周致病菌诱导内源性氧化应激

线粒体通过氧化磷酸化为细胞的各种生命活动提供能源，在此过程中，内源性ROS同步产生[1]。一旦ROS的生成量超出了抗氧化剂所能清除的限度，将导致细胞和组织发生内源性氧化应激而受损[69]。这种损伤可能累及蛋白质、脂质和DNA，并且与炎症、癌症、神经系统疾病等疾病相关[70-72]。线粒体是细胞内源性ROS的主要来源，也是牙周致病菌激活炎症的重要中间介质[73-74]。

牙周致病菌通过诱导线粒体ROS，进而引起细胞功能障碍和异常活动[75-76]。体外实验表明，*P.g*脂多糖能诱导人口腔上皮细胞中ROS和炎症因子TNF-α和IL-β的水平上调[77]。同样，*P.g*脂多糖能诱导人牙龈成纤维细胞中线粒体ROS浓度的升高，而消除线粒体ROS成功抑制了脂多糖诱导的p38/JNK信号通路和NF-κB信号通路，使得炎性因子白细胞介素-1β（interleukin-1β，IL-1β）、白细胞介素-6（interleukin-6，IL-6）和肿瘤坏死因子-α（tumor necrosis factor-α，TNF-α）的表达水平显著下降[73，78]。这表明*P.g*能通过诱导人牙龈成纤维细胞中线粒体ROS表达增加促进牙周炎，还有研究表明，*P.g*诱导的线粒体ROS累积能下调人牙龈成纤维细胞线粒体生物发生，使其细胞活性下降[35]。

此外，*F.n*感染可激活牙龈上皮细胞中炎症小体NLRP3，进而激活caspase-1并上调IL-1β的表达，促进线粒体ROS的产生，而此过程受到NLRX1的正反馈调节[16，79]。

*A.a*通过诱导巨噬细胞ROS增加上调炎性因子IL-1β以及激活炎性小体NLRP3，这有助于维持牙周炎性环境[73，80]。

6　总结与展望

牙周致病菌是牙周炎的始动因子，其感染是牙周炎的发生、发展中的关键环节以及疾病干预的重要靶点。

随着对牙周炎致病机制的深入研究，线粒体在其中的重要作用逐渐凸显。牙周致病菌可以诱导牙周组织细胞中线粒体生物发生紊乱、干扰线粒体动力学、抑制线粒体自噬以及抑制牙周组织细胞发生线粒体相关性细胞凋亡，引起缺陷线粒体的累积、线粒体ROS和DNA的外泄，最终导致线粒体功能障碍，促进牙周炎症。此外，牙周致病菌还能促进免疫细胞线粒体相关性细胞凋亡，有助于病菌逃逸机体免疫清除作用（图1）。

目前研究主要集中在*P.g*、*A.a*和*F.n*对于线粒体的影响，其它牙周致病菌对于线粒体是否具有相似的影响尚未明确。牙周致病菌诱导线粒体功能障碍的具体机制仍需进一步探索，这对挖掘新的牙周炎控制靶点具有重要意义。基于线粒体参与牙周致病菌促炎机制的具体作用，靶向线粒体功能功能可能成为牙周炎治疗的潜在切入点。

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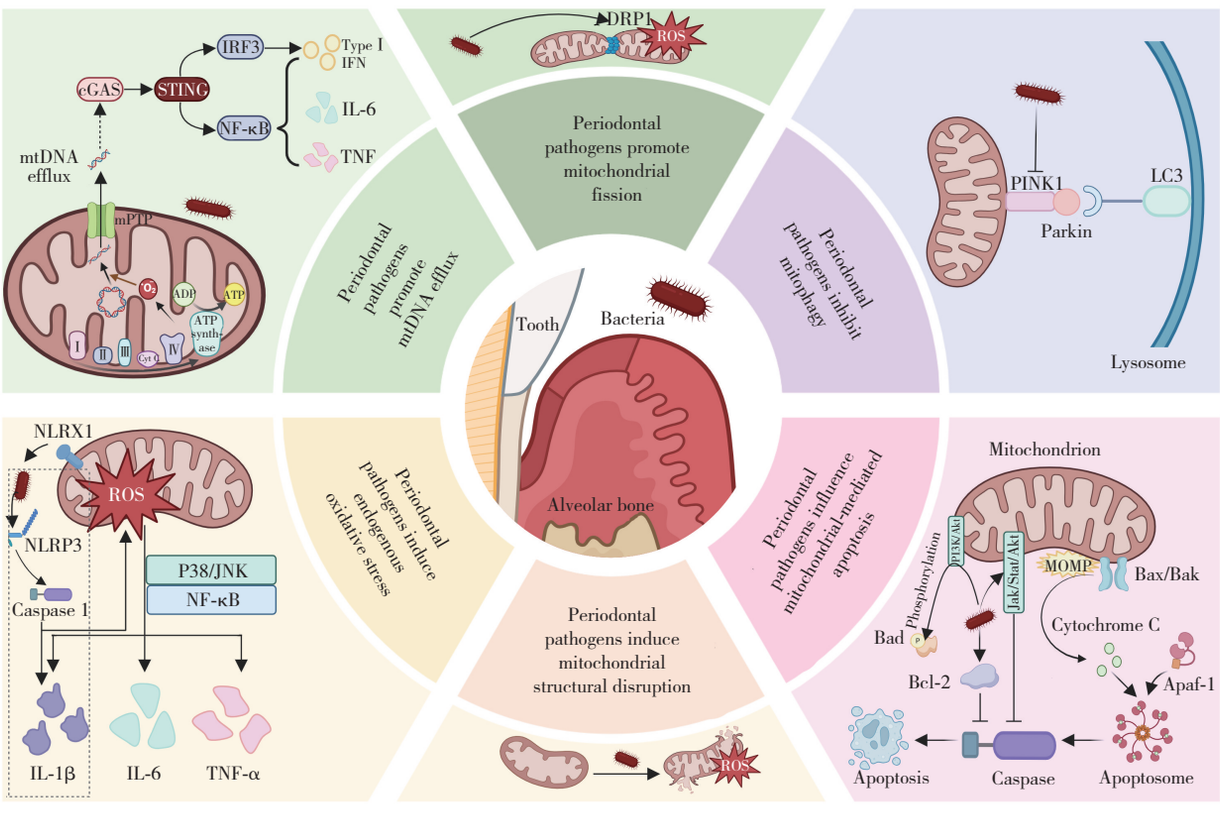

mtDNA: mitochondrial DNA; DRP1: dynamin-related protein 1 (mediates mitochondrial fission); LC3: microtubule-associated protein 1 light chain 3 (autophagy marker); IL-1β: interleukin-1β; IL-6: interleukin-6; TNF-α: tumor necrosis factor-α; Type Ⅰ INF: type Ⅰ interferons; NLRP3: nucleotide-binding oligomerization domain-like receptor protein 3 (inflammasome); NLRX1: NOD-like receptor family member X1; MOMP: mitochondrial outer membrane permeabilization; Bcl-2: B-cell lymphoma 2 protein (anti-apoptotic protein); Bax/Bak: Bcl-2-associated X protein/Bcl-2 homologous antagonist killer (form oligomeric pores in mitochondrial outer membrane); Bad: Bcl-2-associated death promoter (pro-apoptotic protein); Cytochrome C: respiratory chain component; Apaf-1: apoptotic protease-activating factor-1 (forms apoptosome with cytochrome c); Caspase: cysteine-aspartic protease (apoptosis executioner); Created with BioRender.com

Figure 1　Mechanisms of periodontal pathogen-induced mitochondrial dysfunction in the promotion of periodontitis

图1　牙周致病菌诱导线粒体功能障碍促进牙周炎机制示意图

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