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牙周炎中炎症–再生失偶联的线粒体基础及其靶向治疗

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摘　要

牙周炎是一种由失衡菌斑驱动、宿主免疫反应失调参与的慢性炎症性疾病，其治疗困难不仅在于炎症持续，更在于炎症控制后牙周组织难以实现有效重建。越来越多的证据提示，牙周炎中存在“炎症消退”与“再生启动”失偶联的困境，而线粒体功能障碍可能是连接两者的重要共同节点。在线粒体异常背景下，巨噬细胞表现为促炎偏向持续化、炎症消退受阻及促破骨活性增强；同时再生相关细胞表现出成骨潜能下降及免疫表型重塑。此外，线粒体功能障碍还可通过改变细胞的代谢适应性、影响旁分泌信号传导等影响细胞间互作，进一步促进细胞间的病理串扰。基于此，线粒体靶向治疗正由单纯的抑炎或促再生，转向从上游的线粒体这一信号枢纽协调炎症消退与组织修复的启动。本文以巨噬细胞–干细胞轴为主线，综述线粒体功能障碍在牙周炎“炎症–再生失偶联”中的作用机制，并总结线粒体靶向治疗的主要策略、研究进展及当前局限，以期为牙周炎骨免疫调控与再生治疗提供综合性视角。

关键词

牙周炎，线粒体功能障碍，巨噬细胞，牙周膜干细胞，线粒体靶向治疗

Mitochondrial Basis of Resolution-Regeneration Uncoupling in Periodontitis and Its Targeted Therapy

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Abstract

Periodontitis is a chronic inflammatory disease driven by dysbiotic plaque and dysregulated host immunity. Its therapeutic challenge lies not only in persistent inflammation, but also in the limited capacity for effective periodontal reconstruction after inflammation is controlled. Increasing evidence suggests that periodontitis is characterized by uncoupling of resolution-regeneration, and mitochondrial dysfunction may serve as a key shared node linking these processes. Under mitochondrial stress, macrophages exhibit sustained pro-inflammatory polarization, impaired inflammatory resolution, and enhanced osteoclastogenic activity, whereas regenerative cells show reduced osteogenic potential and reshaped immunophenotypes. In addition, mitochondrial dysfunction may further sustain pathological crosstalk by altering metabolic adaptation, paracrine signaling, and intercellular interactions. Consequently, mitochondria-targeted interventions are shifting from simple anti-inflammatory or pro-regenerative approaches toward coordinated regulation of inflammatory maintenance and tissue repair at an upstream mitochondrial level. Focusing on the macrophage-stem cell axis, this review summarizes the mechanisms by which mitochondrial dysfunction contributes to the uncoupling of resolution-regeneration in periodontitis, and discusses the major mitochondria-targeted therapeutic strategies, recent advances, and current limitations, aiming to provide a comprehensive perspective for osteoimmunomodulation and regenerative therapy in periodontitis.

Keywords

Periodontitis, Mitochondrial Dysfunction, Macrophages, Periodontal Ligament Stem Cells, Mitochondria-Targeted Therapy

1. 引言

牙周炎是一种由菌斑生物膜失衡与宿主异常免疫反应共同驱动的慢性炎症性疾病，最终导致牙周支持组织的进行性破坏[1] [2]。然而，这一以“感染–炎症–组织损伤”为核心的病理框架，主要解释的是疾病发生与进展过程，对于炎症负荷下降后牙周组织仍难实现可预测的功能性再生，解释力仍然有限[3]-[5]。在生理状态下，炎症并非被动终止，而是通过主动消退程序与组织修复相耦联，最终推动稳态恢复[3] [6]；而在牙周炎中，这一协调过程受到破坏，导致局部长期表现为炎症迁延与再生不足并存[4] [7]，本文将该状态概括为“炎症–再生失偶联”。

“失偶联”之所以难以自发纠正，关键在于炎症细胞与再生细胞之间形成了双向的病理串扰[8]。持续偏向促炎表型的免疫细胞不断放大炎症与骨吸收信号[9] [10]，而受炎症重塑的牙周干/祖细胞则表现出成骨和免疫调节功能下降，并可反向参与局部炎症维持，最终形成炎症迁延与再生受限的正反馈环路[11] [12]。在这一过程中，线粒体功能障碍正日益被视为连接炎症失衡与再生受限的重要枢纽。在牙周炎持续存在的炎症微环境中，病原相关刺激、炎症介质和氧化应激可共同破坏线粒体稳态，诱发线粒体活性氧(Mitochondrial Reactive Oxygen Species, mtROS)失衡、线粒体 DNA (mtDNA)外泄、代谢重编程及线粒体质量控制障碍，在疾病进展过程中于不同细胞群体中引发功能异常，此外，线粒体损伤还可增强局部促炎反应，从而促进炎症细胞与再生细胞之间病理串扰的维持，使“炎症–再生失偶联”更易迁延[13]-[15]。

尽管近年来关于牙周炎中线粒体功能障碍的研究迅速积累，现有综述仍多分别侧重于病原相关损伤、特定细胞类型、线粒体机制分支或干预策略。基于此，本文拟以巨噬细胞与干细胞的相互作用为切入点，综述牙周炎中炎症细胞与再生细胞如何形成持续性的病理串扰，分析线粒体功能障碍在驱动“炎症–再生失偶联”中的重要作用，并进一步讨论靶向线粒体治疗在打破这一病理闭环、重塑骨免疫平衡及促进牙周组织功能性再生中的潜力。

2. 线粒体功能障碍驱动巨噬细胞促炎持续化并阻碍炎症消退

正常情况下，巨噬细胞应在初级应答后转入促消退/促修复状态；而持续炎症中的线粒体功能障碍会削弱其代谢可塑性，阻碍其由促炎状态向修复状态转换[16]。这一病理偏向首先建立在免疫代谢重编程失衡之上：持续炎症刺激及线粒体功能受损共同抑制巨噬细胞氧化磷酸化，并推动其代谢由氧化磷酸化(Oxidative Phosphorylation)向糖酵解偏移；与此同时，三羧酸循环在多个关键节点发生重塑，导致琥珀酸等中间代谢物积聚[17] [18]。

在此基础上，巨噬细胞的线粒体功能障碍进一步外化为炎症放大与骨吸收增强。琥珀酸可通过抑制脯氨酰羟化酶稳定 HIF-1α，诱导 IL-1β 等炎症相关基因表达[17]；呼吸链受损及代谢重编程可导致 mtROS 增加，并促进 NF-κB、NLRP3 炎症小体及相关促炎转录程序的激活[19]；受损线粒体释放的 mtDNA 等线粒体来源危险信号损伤相关分子模式(Damage-Associated Molecular Patterns, DAMPs)可激活 GAS-STING、TLR9 等相关先天免疫通路，进一步维持局部炎症输出[20]；线粒体代谢异常还可能通过影响染色质修饰和表观遗传调控，促进促炎转录程序的维持[21]。由此，线粒体不再只是代谢受损的受害者，而成为将细胞内代谢紊乱转化为持续炎症信号的重要节点。与此同时，促炎偏向的巨噬细胞可通过 TNF-α、IL-1β、IL-6 等介质，并在部分情境下伴随 RANKL 相关信号，塑造促破骨微环境[22] [23]；而积聚的琥珀酸也可能通过 SUCNR1 参与破骨分化和骨吸收[24]。除此之外，线粒体功能障碍相关的氧化应激还会损害成骨细胞及其前体的存活和分化，抑制骨形成，从而共同推动牙周骨破坏的持续[25] [26]。

更关键的是，线粒体质量控制失衡会显著削弱巨噬细胞进入炎症消退程序的能力。生理状态下，线粒体自噬(Mitophagy)可清除受损线粒体，限制 mtROS 和 DAMPs 的持续积累，从而维持巨噬细胞的代谢稳态与表型可塑性[27]；与此同时，巨噬细胞通过胞葬作用(Efferocytosis)清除局部凋亡细胞，这是促炎反应向促消退/促修复状态转换的关键步骤[28]。在牙周炎及相关炎性骨丢失环境中，保护性的 PINK1/Parkin 等介导的线粒体自噬可出现功能不足，伴随受损线粒体积累、ROS 升高和炎症信号放大；而巨噬细胞的胞葬能力下降，可进一步妨碍其促消退重编程[29] [30]。因而，自噬失衡与胞葬受损并不只是“清除障碍”的受损，而是共同促成巨噬细胞促炎偏向的持续化，并限制炎症消退与组织修复的启动。

综合来看，线粒体功能障碍导致的核心病理变化，可概括为巨噬细胞由具有较高可塑性的炎症应答细胞，转变为代谢重编程失衡、促炎偏向持续化且再极化受阻的病理效应细胞。其一方面持续输出促炎和促骨吸收信号，另一方面削弱炎症消退及修复启动所需的功能转换，从而在细胞层面为牙周炎“炎症持续–再生受阻”的状态提供了重要的机制基础之一。

3. 线粒体功能障碍驱动 PDLSCs 再生受限并重塑免疫表型

在生理稳态下，以牙周膜干细胞(Periodontal Ligament Stem Cells, PDLSCs)为代表的牙周相关间充质干细胞(Mesenchymal Stem Cells, MSCs)是兼具组织修复与免疫调节能力的牙周稳态维持细胞[31]。线粒体在 PDLSCs 中发挥着代谢调控与信号整合的重要作用，通过调控细胞代谢、线粒体质量控制，参与 PDLSCs 的命运决定、成骨分化和功能维持，因此，当炎症微环境持续诱发线粒体稳态失衡时，PDLSCs 的病理改变表现为免疫调节功能受损与再生执行能力下降并存。

在再生功能方面，线粒体生物能量障碍是 PDLSCs 成骨受损的重要代谢基础之一。电子传递链功能下降和氧化磷酸化受限常伴随 ATP 生成减少，并与成骨相关基因表达下降、基质矿化减弱及分化程序受阻相关[32] [33]；与此同时，线粒体动力学失衡和自噬不足会导致受损线粒体积聚，进一步破坏线粒体质量控制，削弱 PDLSCs 的成骨潜能及其对炎症/氧化应激的适应能力，从而不利于组织修复程序的有序启动[34] [35]。

在免疫表型上，线粒体功能障碍可能使 PDLSCs 的角色由“炎症缓冲者”逐步转向“炎症参与者”。现有研究提示，PDLSCs 的免疫调节能力与代谢重编程密切相关，PGE2-IDO 等免疫调节轴可受代谢状态变化显著影响，因此，当线粒体–代谢稳态遭到持续破坏时，PDLSCs 诱导巨噬细胞向促消退表型转换的能力很可能随之下降[36]。随着损伤累积，PDLSCs 还可能进一步转向异常的炎症输出状态：炎症性 PDLSCs 来源外泌体已被证实可驱动巨噬细胞向 M1 样表型偏移[37] [38]，而持续的氧化应激、衰老相关分泌表型及炎症性细胞死亡则可能进一步放大这一趋势[39] [40]。

综上，线粒体功能障碍对 PDLSCs 的影响，不宜仅概括为“再生受阻”，而是再生能力受损与免疫表型异化并存的功能重塑：其既限制成骨分化和组织修复，又削弱免疫缓冲并可能增强异常炎症输出，最终在局部微环境层面共同推动牙周炎“炎症持续–再生停滞”的长期维持。

4. 线粒体靶向治疗重塑“炎症–再生”耦联

综上，无论是巨噬细胞因线粒体功能障碍驱动的促炎持续化，还是 PDLSCs 因线粒体稳态失衡而出现的成骨受限与免疫表型重塑，均提示线粒体异常并非牙周炎中的伴随现象，而是推动“炎症持续”与“再生受阻”的重要共同节点。基于这一认识，近年的研究已逐步将治疗视角由单纯抑炎或促再生，转向对线粒体功能障碍本身的纠正。

现有研究所涉及的线粒体靶向策略，大体可归纳为线粒体靶向抗氧化、代谢重编程调控、线粒体质量控制恢复、线粒体来源危险信号阻断以及线粒体递送/补充等几类，其共同思路是在上游代谢–信号枢纽层面同时干预炎症维持机制与再生能量基础，从而为打断慢性炎症微环境中“炎症放大–修复受阻”的恶性循环提供新的机制性切入点，但目前证据仍主要来自前临床研究[13] [41] [42]。

从具体策略看，线粒体靶向抗氧化与膜稳态调控是目前研究最广、临床证据相对较多的一类，代表性药物如 MitoQ、Elamipretide 等，其主要机制在于降低 mtROS、稳定线粒体内膜及心磷脂、改善呼吸链电子传递与 ATP 生成，从而减轻线粒体氧化损伤及其继发性炎症放大[42] [43]；代谢重编程干预则聚焦于巨噬细胞糖酵解增强和氧化磷酸化受抑的代谢状态，通过 AMPK 及相关代谢通路调节细胞促炎偏向，在部分研究中改善 MSCs 的代谢稳态与成骨能力，二甲双胍可作为代表性药物之一[44] [45]；质量控制恢复聚焦于恢复线粒体自噬、线粒体生物发生及分裂/融合平衡，减少受损线粒体积累，恢复线粒体网络更新与功能稳态[43] [46]；危险信号阻断则主要针对 mtDNA 外泄、mtROS 过量及其介导的 cGAS-STING、NLRP3 等炎症通路激活，从源头削弱线粒体损伤向持续性炎症信号的转化[47] [48]；与上述“减损”策略相比，线粒体转移、线粒体移植及相关递送策略代表了更具重建导向的新方向，其目标是向受损细胞定向补充功能性线粒体或重建有利的代谢协同，从而推动干预由“减轻损伤”进一步延伸至“补充功能”和“恢复代谢适配”[49]。

总体而言，现有线粒体靶向治疗打破炎症细胞与干细胞病理串扰的机制，大体可归纳为三条主线：其一，减轻巨噬细胞线粒体损伤相关的代谢重编程失衡及 tDNA/mtROS 等危险信号释放，并进一步抑制其对再生细胞的持续抑制；其二，恢复干细胞的线粒体稳态与氧化代谢适配，改善其成骨及免疫调节能力；其三，通过优化旁分泌信号输出、改善细胞间代谢协同，或定向补充功能性线粒体，重塑炎症细胞与再生细胞之间更有利于修复的互作关系。由此，线粒体靶向早治疗的意义并不局限于改善单一细胞器

功能，而在于从上游代谢–信号节点同时影响免疫代谢与再生代谢过程，从而为逆转慢性炎症相关的组织破坏和修复障碍提供一种有前景的机制性思路。

尽管线粒体靶向治疗已显示出同时调控炎症反应与组织再生的潜力，但该领域总体仍处于由概念验证迈向精准转化的过渡阶段。基于已有的前临床有效性证据，当关注的问题正逐步转向：不同线粒体靶向策略主要作用于牙周炎病程的哪一层级，适用于何种局部微环境与优势靶细胞，及其能否有效重塑巨噬细胞–干细胞串扰中的炎症代谢失衡、细胞间通讯紊乱与再生受抑状态。然而，现有相关工作仍多以单一细胞类型、单一机制通路或单一结局指标为切入点，针对不同策略适用阶段与适应场景的直接比较研究仍然不足，递送与疗效评价体系也尚未完全标准化。需要认识到，在牙周这一同时受唾液、龈沟液冲刷及生物膜屏障影响的开放性动态病灶中，线粒体靶向治疗能否转化为稳定的临床获益，仍在很大程度上受限于局部的药物递送效能。

5. 线粒体靶向治疗牙周炎的工程化解决方案、转化挑战与未来方向

牙周局部属于开放且动态的病理环境，持续的唾液与龈沟液流动会削弱药物滞留，而生物膜和炎症相关氧化应激等因素又进一步增加了局部治疗穿透与稳定释放的难度[50] [51]。因此，面向牙周微环境，设计具备响应性释放、局部富集与抗冲刷能力的智能药物递送系统，为线粒体靶向治疗实现同步调控炎症微环境、氧化应激与再生过程的目标提供了更具操作性的实施路径[52] [53]。

现阶段针对牙周炎的局部智能递送体系，大致可分为三类设计逻辑：其一，微环境响应递送，即利用牙周病灶特异性的病理信号(如微酸性 pH、ROS 过载及相关酶活化等)作为“开关”，实现药物在局部的可控触发[54] [55]；其二，靶向富集型递送，即通过配体修饰、表面功能化或仿生膜包裹等方式，提高药物在相应靶细胞、生物膜或炎症相关微环境中的选择性分布，或结合细胞器导向设计，增强药物的胞内递送及对线粒体等亚细胞器的定位能力[56]；其三，功能集成型递送，即在同一平台中整合抗菌、免疫调控、促再生，乃至诊断监测等多重功能[57] [58]。上述思路并不与单一载体一一对应，而是依托不同材料平台实现，目前较常见的载体主要包括水凝胶、纳米颗粒及纳米–水凝胶复合系统等，纤维/纳米纤维类体系亦有报道。

尽管智能递送体系为线粒体靶向治疗提供了更具选择性的实施路径，但其进一步转化仍面临若干现实限制。首先是体内外微环境的显著差异：牙周袋内信号具有高时空异质性，体外表现优异的响应型材料在真实病理生境中，因信号重叠、微环境动态波动等原因，常遭遇局部滞留不足、突释或脱靶等，导致预期疗效被削弱[53]。其次是工程化放大与规模制造的瓶颈：随着功能模块不断叠加，智能平台在制备工艺和质量控制方面的复杂性同步增加，这直接导致规模化生产困难、批次间一致性难以保障，尚未展现出清晰的临床成本效益优势[57] [59]。另外是远期生物安全性的证据缺失：当前安全性评价仍以短期生物相容性和急性毒性观察为主，对于长期局部滞留、材料降解行为、重复给药以及慢性暴露条件下的组织反应，仍缺乏系统验证。因此，智能递送体系后续发展的重点，不应仅停留于提高响应性和功能集成度，更应转向局部适配性、标准化质控、长期安全性与临床可实施性的综合提升。

总体而言，线粒体功能障碍为理解牙周炎中炎症持续与再生受阻的并存状态提供了整合视角，也为干预巨噬细胞–干细胞病理串扰提供了潜在切入点。进一步提升线粒体靶向治疗的转化意义，有赖于将线粒体靶点、病程分期、靶细胞选择与局部智能递送体系有机整合，推动策略由前临床验证走向更精准、可实施的牙周治疗方案。

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