[DOI]10.12016/j.issn.2096-1456.202330511

·综述·

牙周炎中巨噬细胞极化、焦亡、胞葬的研究进展

贺欣然[1]，　李元[1]，　张武阳[1]，　安莹[2]，　薛洋[1]
1. 口颌系统重建与再生全国重点实验室，国家口腔疾病临床医学研究中心，陕西省口腔疾病临床医学研究中心，空军军医大学口腔医院颌面外科，陕西 西安(710032)；　2. 口颌系统重建与再生全国重点实验室，国家口腔疾病临床医学研究中心，陕西省口腔疾病国际联合研究中心，空军军医大学第三附属医院牙周病科，陕西 西安(710032)

【摘要】 牙周炎导致牙周组织发生不可逆性破坏是外在致病因素与内在免疫应答失衡的结果。巨噬细胞作为人体免疫细胞，在牙周炎的发生发展中发挥促炎与抗炎双重作用。患者牙周组织微环境内的病原菌、炎症因子、中性粒细胞可显著影响巨噬细胞代谢和功能状态，而巨噬细胞的状态又能反过来调节疾病进程。病原菌通过激活NF-κB信号通路促使巨噬细胞向M1促炎型极化并发生焦亡，进而形成诱导牙周组织破坏的微环境。随着牙周炎的发展，大量凋亡中性粒细胞被巨噬细胞识别、吞噬(胞葬)，该过程能够抑制NF-κB信号通路，同时激活核受体PPAR、LXR，利于向M2抗炎型极化并进一步增强巨噬细胞胞葬活性，从而限制组织炎症性损伤并促进修复。近年来以调节巨噬细胞为核心的牙周炎治疗策略得到了广泛关注，具体手段包括基因敲除、纳米粒子、外泌体、miRNA、多不饱和脂肪酸饮食等等。本文就巨噬细胞极化、焦亡、胞葬与牙周炎的关系进行综述，为牙周炎的治疗提供参考。

【关键词】 牙周炎；　巨噬细胞；　固有免疫；　极化；　焦亡；　胞葬；　代谢重编程；　炎症小体；　NF-κB信号通路
【中图分类号】 R78　【文献标志码】 A　【文章编号】 2096-1456(2024)11-0886-08
【引用著录格式】 贺欣然，李元，张武阳，等. 牙周炎中巨噬细胞极化、焦亡、胞葬的研究进展[J]. 口腔疾病防治，2024，32(11)：886-893. doi:10.12016/j.issn.2096-1456.202330511.

微信公众号

Research progress on macrophage polarization, pyroptosis, and efferocytosis in periodontitis

HE Xinran[1], LI Yuan[1], ZHANG Wuyang[1], AN Ying[2], XUE Yang[1]. 1. State Key Laboratory of Oral & Maxillofacial Reconstruction and Regeneration, National Clinical Research Center for Oral Diseases, Shaanxi Clinical Research Center for Oral Diseases, Department of Oral and Maxillofacial Surgery, School of Stomatology, The Fourth Military Medical University, Xi′an 710032, China; 2. State Key Laboratory of Oral & Maxillofacial Reconstruction and Regeneration , National Clinical Research Center for Oral Diseases , Shaanxi Clinical Research Center for Oral Diseases, Department of Periodontology , School of Stomatology , The Fourth Military Medical University, Xi′an 710032, China
Corresponding author: XUE Yang, Email: xueyangfmmu@163.com, Tel: 86-13310984292

【Abstract】 The irreversible destruction of periodontal tissue caused by periodontitis is the result of an imbalance between external pathogenic factors and the internal immune response. As human immune cells, macrophages have both pro- and anti-inflammatory roles in the occurrence and development of periodontitis. Pathogenic bacteria, inflammatory cytokines, and neutrophils in the periodontal microenvironment can significantly affect the metabolism and functional status of macrophages, and the status of macrophages can regulate disease processes. By activating the NF-κB signaling pathway, the bacteria cause macrophages to undergo M1 proinflammatory polarization and pyroptosis, forming a microenvironment that induces periodontal tissue destruction. With the development of the disease, numerous apoptotic neutrophils are recognized and phagocytized by macrophages (i.e. efferocytosis), which can both inhibit the NF-κB pathway

【收稿日期】2023-10-27；　【修回日期】2024-02-03
【基金项目】陕西省青年科技新星创新能力支撑计划(2022KJXX-100)
【作者简介】贺欣然，学士，Email：2834710015@qq.com，Tel：86-15339093394
【通信作者】薛洋，副教授，博士，Email：xueyangfmmu@163.com,，Tel: 86-13310984292

and activate the nuclear receptors PPAR and LXR, promoting the anti-inflammatory polarization of M2 and further enhancing the efferocytosis activity of macrophages. As a result, these treatments can limit tissue inflammatory damage and promote tissue repair. In recent years, periodontitis treatment strategies focusing on macrophage regulation have received extensive attention, including gene knockout, nanoparticles, exosomes, miRNA, and polyunsaturated fatty acid diets. In this article, we review the specific role of macrophages in periodontitis from three aspects, including macrophage polarization, pyroptosis, and efferocytosis, which may improve our understanding of periodontitis and provide possible directions for periodontitis treatment strategies.

【Key words】 periodontitis; macrophage; innate immunity; polarization; pyroptosis; efferocytosis; metabolic reprogramming; inflammasome; NF-κB signaling pathway

J Prev Treat Stomatol Dis, 2024, 32(11): 886-893.

【Competing interests】 The authors declare no competing interests.

This study was supported by the grants from Young Star of Science and Technology Innovation Ability Support Plan of Shaanxi (No. 2022KJXX-100).

牙周炎是一种多因素参与的慢性炎症性疾病[1]，患病率为62%[2]，如何有效控制疾病进展是亟待解决的问题[3]。在牙周组织发生感染时，作为机体的固有免疫细胞，巨噬细胞在牙龈卟啉单胞菌脂多糖（lipopolysaccharides，LPS）刺激下向M1促炎型极化，以帮助宿主对抗病原体。随着疾病发展，会有更多巨噬细胞向M2抗炎型极化，参与组织修复。巨噬细胞通过调节自身极化、焦亡、胞葬状态，发挥着吞噬病原菌、清除凋亡细胞、分泌炎症因子、刺激骨吸收等多重作用，因而与牙周炎病程进展密切相关。目前通过调控巨噬细胞极化、焦亡、胞葬状态进行牙周炎治疗是研究热点。本文就巨噬细胞极化、焦亡、胞葬与牙周炎的关系进行综述，为牙周炎的治疗提供参考。

1　巨噬细胞极化与牙周炎的关系

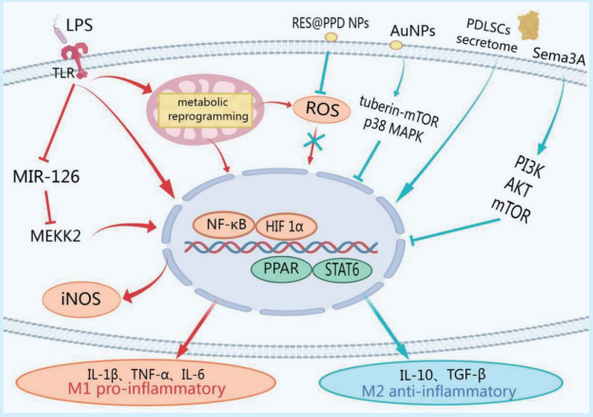
巨噬细胞具有异质性，根据功能可分为促炎型（M1型）和抗炎型（M2型）。巨噬细胞极化是一个动态、连续过程，M1、M2是极化的两种极端情况。微环境发生变化时，巨噬细胞可迅速从M1型转变为M2型，反之亦然[4]。极化状态与特征性的代谢通路密切相关。正常条件下，巨噬细胞通过三羧酸循环产生能量以满足生理需求，但经LPS体外刺激后，巨噬细胞进行代谢重编程，转变为依赖糖酵解产能[5]，进而向M1极化。增强巨噬细胞氧化磷酸化或抑制糖酵解均可实现M1向M2的转变[6]。代谢重编程过程除了伴随巨噬细胞表型的转换，还有大量以柠檬酸、琥珀酸为代表的中间产物产生[7]，其可进一步调控炎症相关基因白细胞介素1β（interleukin-1β，IL-1β）的表达[8]，参与调控炎症过程（图1）。

动物和临床研究均发现，慢性牙周炎牙龈组织样本中M1型巨噬细胞特异性标志物诱导一氧化氮合酶（inducible nitric oxide synthase，iNOS）和信号传导和转录激活因子1（signal transducer and activator of transcription 1，STAT1）的水平显著升高且慢性牙周炎患者的龈沟液更利于单核细胞的浸润与M1极化[9-10]，提示M1参与了牙周炎症反应和组织损伤。当通过基因敲除（C3ar或Cth基因）或功能抑制等方式阻断M1极化时，小鼠实验性牙周炎也可被阻断[11-12]。

M2型巨噬细胞可分泌白细胞介素10（interleukin-10，IL-10）、转化生长因子β（transforming growth factor-β，TGF-β）等抗炎因子，参与牙周组织的免疫调节和再生修复，因而有学者认为M1/M2的比例失衡亦是导致牙周炎的重要因素。研究发现牙周炎牙龈组织中M1型巨噬细胞比例增高，而M2型巨噬细胞比例较低，M1/M2比值高于健康组织[12]。据此有学者将M2型巨噬细胞注射到牙周炎小鼠的龈沟内，使M1/M2比值接近于健康牙周组织水平[13]，结果有效缓解了牙周炎症状。

目前，大量研究尝试通过调控巨噬细胞极化，达到改善炎症微环境、抑制骨质丢失、促进骨形成的目标[14]，例如，局部应用金纳米粒子（AuNPs）[15]、白藜芦醇和20（S）-原醇二醇复合纳米粒子（RES@PPD NPs）[16]、外泌体[17]、脑信号蛋白3A（Sema3A）[18]或miR-126模拟物[19]等。其中，纳米粒子经胞吞进入巨噬细胞内部直接调节细胞代谢，miR-126模拟物靶向抑制蛋白激酶MEKK2，二者均可显著抑制M1型巨噬细胞NF-κB通路。脑

信号蛋白3A则是通过激活PI3K/AKT/mTOR，促进更多巨噬细胞向M2极化。此外，上述物质亦可通过清除活性氧（reactive oxygen species，ROS）[16]、促进巨噬细胞分泌骨形态发生蛋白2[15]或趋化因子[17]等方式调节宿主免疫，有效缓解组织损伤（图1）。但是，通过调节巨噬细胞极化状态治疗牙周炎的策略目前仍处于探索阶段且存在一定争议。部分学者认为动物模型来源的巨噬细胞极化状态与人类存在差异[20]。巨噬细胞的极化状态依赖于局部微环境[21]，而这种环境在体外难以完全模拟。此外，外源物质调节巨噬细胞极化状态的具体机制仍不明晰，增加了药物研究的复杂性。



Lipopolysaccharide (LPS) transmits signals by binding to Toll-like receptors, which can activate transcription factors NF-κB and HIF 1α directly or indirectly to participate in gene regulation, and then promotes the release of pro-inflammatory cytokines such as IL-1β, TNF-α, and IL-6, leading to M1 polarization (red lines). The external substances miR-126, RES@ PPD NPs, AuNPs, and Sema3A could block the excessive release of proinflammatory cytokines by inhibiting the transcription factors NF-κB and HIF 1α. PDLSC secretomes can stimulate the nuclear receptor PPAR and transcription factor STAT6, increasing the release of IL-10 and TGF-β and promoting M2 polarization (green lines), which play a therapeutic role in periodontitis. TLR: toll-like receptor; HIF 1α: hypoxia inducible factor 1α; IL-1β: interleukin-1β; TNF-α: tumor necrosis factor receptor-α; IL-6: interleukin-6; MIR-126: microRNA-126; MEKK2: mitogen-activated protein kinase kinase kinase 2; RES @ PPD NP: resveratrol nanoparticles loaded with 20(S)-protopanaxadiol; AuNPs: gold nanoparticles; Sema3A: semaphorin 3A; PI3K: phosphatidylinositide3-kinases; AKT: protein kinase B; mTOR: mammalian target of rapamycin; PDLSCs: periodontal ligament stem cells; ROS: reactive oxygen species; MAPK: mitogen-activated protein kinase; iNOS: inducible nitric oxide synthase; PPAR: peroxisome proliferator activated receptor; STAT6: signal transducer and activator of transcription 6; IL-10: interleukin-10; TGF-β: transforming growth factor-β

Figure 1　Relationship between macrophage polarization and periodontitis

图1　巨噬细胞极化与牙周炎的关系

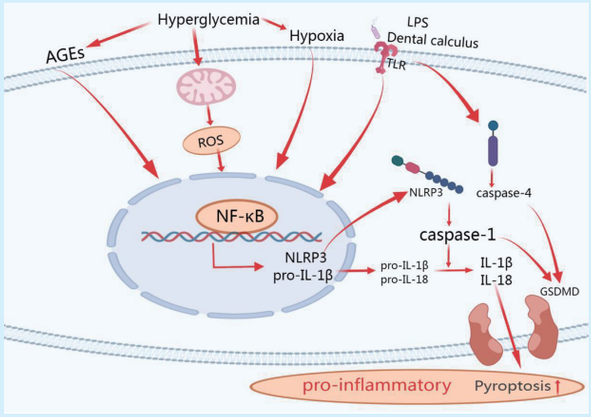
2　巨噬细胞焦亡与牙周炎的关系

细胞焦亡是一种由炎症小体介导的程序性细胞死亡方式，是机体固有免疫应答的重要组成部分。NLRP3作为一种经典炎症小体，通过NLRP3模式识别受体识别微生物结构并激活效应蛋白caspase-1，促进细胞焦亡发生并伴随大量IL-1β和IL-18的释放（图2）。焦亡时，细胞发生裂解，从而限制了病原体在细胞内的生存和增殖[22]，伴随释放的炎症因子可进一步调节免疫细胞趋化及细胞因子的产生。然而，过量的炎症因子会激发骨吸收等牙周组织破坏行为[23]，而在动物模型上抑制巨噬细胞焦亡可一定程度上缓解牙周炎症[24]，提示焦亡与牙周炎密切相关。

临床研究发现，牙周炎患者牙龈组织中NLRP3 mRNA水平是健康受试者的4.3倍，且炎症因子IL-1β、IL-18的水平与NLRP3水平呈正相关[25]。利用牙龈卟啉单胞菌体外刺激人单核细胞后，NLRP3 mRNA水平随细菌量的增加而增加[25]。研究发现牙龈卟啉单胞菌可通过激活巨噬细胞内的NLRP3促进焦亡，引发牙周组织的病理性损伤；且敲除牙周炎小鼠Nlrp3基因可使炎症因子分泌减少，骨保护素增加，牙槽骨吸收症状得到有效缓解[26]。这说明牙周炎条件下，巨噬细胞过度焦亡会导致牙周组织损伤。非经典焦亡途径也参与了牙周炎的发生、发展。牙周炎患者的牙周组织中caspase-4被异常激活[27]，且阻断非经典凋亡途径，减轻牙周组织损伤[28]（图2）。

研究证实体内血糖水平与牙周炎的进展和组织破坏程度呈正相关[29]，可能与牙龈组织中NLRP3炎症小体介导的巨噬细胞焦亡增强有关[30-31]，抑制NLRP3后组织破坏减轻[32]。而糖尿病条件下炎症小体活性增加的原因可能与高血糖导致的缺氧环境以及晚期糖基化产物蓄积有关[33]。Shao等[34]研究发现高血糖水平会同时对巨噬细胞表型产生影响，多种配体通过结合细胞表面Toll样受体激活下

游NF-κB信号通路，促进TNF-α等炎症因子释放，发挥促炎功能。高血糖诱发巨噬细胞焦亡，促进炎症因子释放增加，且一定程度上降低其吞噬能力。牙结石作为牙周炎的另一促进因素，其表面始终存在非矿化生物膜，能够捕获大量细菌、病毒、食物残渣等，不断刺激牙龈组织产生炎症。Montenegro等[35]研究发现，牙周炎患者口内牙结石可通过激活人外周血单核细胞焦亡，增加炎症因子IL-1β分泌，从而揭示了牙结石促进牙周炎的一种潜在机制（图2）。



Hyperglycemia can activate the transcription factor NF-κB by AGEs, ROS, and hypoxia. They activate the protease caspase-1 through the classical inflammasome NLRP 3 pathway, leading to macrophage pyroptosis. In addition to the classical inflammasome pathway, LPS can activate non-classical inflammasome caspase-4 directly to promote macrophage pyroptosis, the release of inflammatory cytokines such as IL-1 βand IL-18, and stimulate inflammation. AGEs: advanced glycation end products; TLR: toll-like receptor; ROS: reactive oxygen species; LPS: lipopolysaccharide; NLRP3: NLR family pyrin domain containing 3; pro-IL-1β: interleukin-1β precursors; pro-IL-18: interleukin-18 precursors; IL-1β: interleukin-1β; IL-18: interleukin-18; GSDMD: gasdermin

Figure 2　Relationship between macrophage pyroptosis and periodontitis
图2　巨噬细胞焦亡与牙周炎的关系

3　胞葬作用与牙周炎的关系

牙周炎发病时，中性粒细胞最先被募集到感染部位，发挥抗炎作用后发生凋亡。巨噬细胞识别并吞噬凋亡中性粒细胞的过程被称为胞葬。胞葬发生时，暴露于凋亡细胞表面的磷酯酰丝氨酸（phosphatidylserine，PS）与巨噬细胞表面受体结合，促进胞内吞噬体形成。降解中性粒细胞的过程会释放大量蛋白质、核苷酸、碳水化合物和脂质进入巨噬细胞代谢、能量循环，调节巨噬细胞向抗炎型转换[36-37]。脂肪酸经线粒体氧化后改变了NAD+/NADH平衡，促进巨噬细胞释放抗炎介质[38]；蛋白质代谢过程中产生腐胺协助激活Rac1，可提高巨噬细胞吞噬能力[39]；巨噬细胞糖酵解产生的乳酸在增强自身胞葬活性[40]的同时可调控周围巨噬细胞发挥抗炎作用[41]（图3）。因此胞葬作用对维持组织稳态具有重要意义[42]，不但可以防止大量毒性物质向外释放导致继发性坏死，还可以终止炎症反应、促进自我耐受、激活炎症消散途径。胞葬受损会导致炎症加剧[42]。提示胞葬作用异常与牙周炎的发生、发展密切相关，具体分为细胞募集异常与胞葬作用活性调节异常两大类。

3.1　中性粒细胞/巨噬细胞募集异常

中性粒细胞缺乏所致的胞葬作用降低与牙周炎密切相关。白细胞黏附缺陷-1型（leukocyte adhesion deficiency-type 1，LAD1）是由于ITGB2（CD18）基因突变引起中性粒细胞外周组织募集障碍的一种遗传性疾病[43]。Kajikawa等[44]发现LAD1患者因胞葬作用缺陷无法产生抗炎信号，导致体内IL-23/IL-17轴过度激活，牙龈组织内高水平IL-23/IL-17是引起损伤的直接原因，因此LAD1患者表现为快速进展的牙龈炎及牙周炎。而在$CD18^{-/-}$小鼠牙周炎模型中，通过中性粒细胞移植或直接激活胞葬作用相关受体，可在一定程度上改善牙周炎引发的组织损伤，这也提示激活胞葬作用受体，如：肝X受体（liver X receptor，LXR）、过氧化物酶体增殖物激活受体（peroxisome proliferator activated receptor，PPAR）等，有望成为治疗LAD1患者牙周炎的潜在策略[44]。

中性粒细胞/巨噬细胞过度募集亦可能加重牙周炎。研究发现，干扰素诱导蛋白16（iInterferon-inducible protein 16，IFI16）基因变异会增强人内皮细胞对牙周病原体的反应，分泌更多的中性粒细胞/巨噬细胞趋化因子，导致中性粒细胞/巨噬细胞过度募集，显著增加此类人群牙周炎患病风险和严重程度[45]。Ifi204（小鼠IFI16同源物）$^{-/-}$牙周炎小鼠牙龈组织中IL-1β水平升高，牙槽骨丢失增

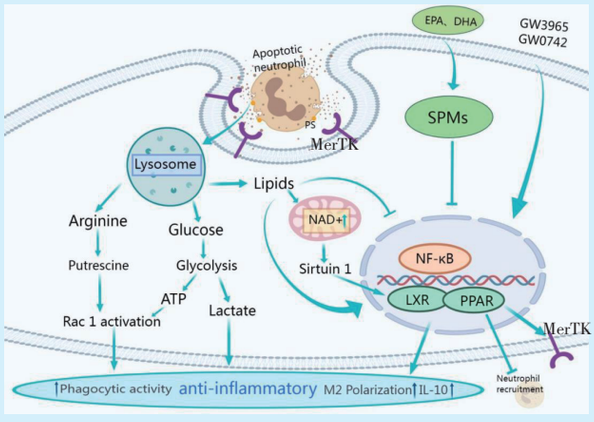
加[46]。由此可知，即使胞葬具有抑制免疫细胞过度募集的作用，但效果有限。倘若无法平衡中性粒细胞过度募集的趋势，牙周组织炎症仍会发生、发展。

3.2　胞葬作用活性调节异常

胞葬作用活性调节异常所致的牙周组织中性粒细胞蓄积是导致牙周组织损伤的重要原因之一，且损伤程度具有明显的个体差异性。

内源性特异性促炎症消退介质（specialized pro-resolving mediators，SPMs）是一类具有强大抗炎潜能物质（脂氧素、保护素、消退素等）的总称，由不饱和脂肪酸代谢生成，在胞葬作用活性调控中发挥重要作用。牙周炎患者唾液中脂氧素A4（lipoxin A4，LXA4）的水平显著降低[47]，提示牙周炎的发生与低水平LXA4所导致的胞葬活性不足有关[48]。Stańdo等[49]发现，非手术治疗期间牙周炎患者通过高剂量的多不饱和脂肪酸饮食提高体内SPMs水平，可显著减少牙周袋深度，并提高临床附着水平[50]（图3）。进一步探究发现，外源RvD2注射可有效降低牙周炎小鼠牙龈组织内促炎细胞因子IFN-γ、TNF-α浓度，促进M2极化的关键蛋白IRF4水平升高并伴随中性粒细胞数量降低[51]。由此推测，通过补充SPMs增强胞葬活性有望成为未来牙周炎治疗的潜在方向。

另外，胞葬过程中巨噬细胞代谢负荷加重，降解凋亡中性粒细胞可激活一系列转录调节因子核受体（即胞葬受体），如：LXRα、LXRβ、PPARγ、PPARδ和RXRα，促进炎症消散。激活的LXR可直接抑制IL-23/IL-17/G-CSF细胞因子级联反应，从而减少中性粒细胞蓄积造成的组织损伤[52]。与此同时，激活PPAR受体能够通过增加巨噬细胞表面凋亡受体MerTK表达进一步提高胞葬活性，同时诱导抗炎基因IL-10表达[53]。动物实验中，将GW3965（LXR激动剂）和GW0742（PPAR激动剂）注射到牙周炎小鼠牙龈组织内，可观察到局部炎症细胞数量减少、骨质丢失减轻[44]。综上，牙周炎的发生可能与调节信号异常所导致的巨噬细胞胞葬活性不足有关，内源性脂质抗炎介质水平下降或胞葬受体激活障碍导致的抗炎信号受损，都有可能促进牙周炎症（图3）。



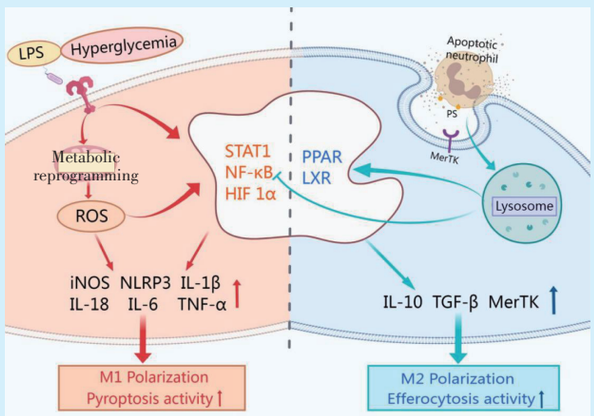
Macrophages recognize phosphatidylserine (PS) on the surface of neutrophils through the MerTK receptor and phagocytize apoptotic neutrophils (i.e. efferocytosis), before decomposing them to produce arginine, glucose, and lipids. The metabolism of arginine and glucose can increase the phagocytosis activity of macrophages. By inhibiting NF-κB and activating the nuclear receptors LXR and PPAR, lipids can promote M2 polarization, inhibit neutrophil recruitment, and increase the expression of IL-10 and MerTK. Exogenous supplementation of polyunsaturated fatty acids such as EPA and DHA leads to their transformation in vivo to produce SPMs that exert anti-inflammatory effects by inhibiting NF-κB, whereas GW3965 (LXR agonist) and GW0742 (PPAR agonist) exert anti-inflammatory effects by activating nuclear receptors directly. MerTK: c-mer proto-oncogene tyrosine kinase; ATP: adenosine triphosphate; Rac 1: ras-related C3 botulinum toxin substrate 1; NAD: nicotinamide adenine dinucleotide; LXR: liver X receptor; PPAR: peroxisome proliferator activated receptor; EPA: eicosapentaenoic acid; DHA: docosahexaenoic acid; SPMs: specialized pro-resolving mediators

Figure 3　Relationship between macrophage efferocytosis and periodontitis

图3　巨噬细胞胞葬与牙周炎的关系

4　结　语

巨噬细胞极化、焦亡、胞葬与牙周炎的发生发展有关（图4）。牙周炎病原菌侵入时，LPS可直接或间接激活核转录因子HIF 1α及NF-κB，诱导下游促炎细胞因子IL-1β、TNF-α合成释放，NF-κB的激活也使NLRP3的表达增加[25]，即巨噬细胞向M1极化的同时焦亡活性增加[5]，从而激发炎症。随着疾病进展，大量凋亡中性粒细胞被巨噬细胞识别、吞噬（即胞葬），该过程激活核受体PPAR、LXR，同时对NF-κB信号通路产生抑制，在减少促炎因子的同时促进IL-10、TGF-β等抗炎因子的分泌，即巨噬细胞向M2极化的同时胞葬活性增加，共同促进牙龈内炎症消散、组织修复。通过外源补充SPMs可同时增强胞葬活性、抑制焦亡并促进M2极



Macrophage polarization, pyroptosis, and efferocytosis are all involved in the occurrence and development of periodontitis, and there are mutual and inseparable regulatory mechanisms among them. LPS, hyperglycemia, and other external factors can stimulate the metabolic reprograming of macrophages and activate a series of transcription factors (STAT1, NF-κB, HIF-1α), which promote iNOS synthesis, an increase in NLRP3, and the release of a variety of proinflammatory cytokines, thus promoting an increase in the pyroptosis activity of macrophages and M1 polarization (left side). In contrast, after phagocytizing and metabolizing apoptotic neutrophils, the metabolites in macrophages promote the synthesis and secretion of anti-inflammatory cytokines by activating nuclear receptors (PPAR, LXR) and inhibiting NF-κB, thereby further enhancing the efferocytosis activity of macrophages and promoting M2 polarization (right side). LPS: lipopolysaccharides; PS: phosphatidylserine; MerTK: c-mer proto-oncogene tyrosine kinase; ROS: reactive oxygen species; STAT1: signal transducer and activator of transcription 1; HIF-1α: hypoxia inducible factor-1α; iNOS: inducible nitric oxide synthase; PPAR: peroxisome proliferator activated receptor; LXR: liver X receptor; iNOS: inducible nitric oxide synthase; NLRP3: NLR family pyrin domain containing 3; IL-1β: interleukin-1β; IL-18: interleukin-18; TNF-α: tumor necrosis factor receptor-α; IL-10: interleukin-10; TGF-β: transforming growth factor-β

Figure 4　Relationship between macrophage polarization, pyroptosis, efferocytosis, and periodontitis

图4　牙周炎进程中巨噬细胞极化、焦亡、胞葬之间的关系

化[54-55]，从而缓解临床症状。因此，削弱M1促炎作用，调节巨噬细胞极化至平衡状态[15-19]；抑制巨噬细胞焦亡，避免促炎因子大量释放[27-29]；调节胞葬活性达正常水平[49-51]等治疗策略应运而生。但面临的主要问题是巨噬细胞功能状态的具体调控机制仍不明晰；外源物质参与调节巨噬细胞的效果受多因素干扰，且调节巨噬细胞向抗炎状态发展，在减轻组织损伤的同时是否带来了细菌增殖扩散的不利影响仍需进一步明确。

【Author contributions】 He XR collected the references, conceptualized and wrote the article. Li Y and Zhang WY revised the article. An Y and Xue Y conceptualized and reviewed the article. All authors read and approved the final manuscript as submitted.

参考文献

[1] Kwon T, Lamster IB, Levin L. Current concepts in the management of periodontitis [J]. Int Dent J, 2021, 71(6): 462-476. doi: 10.1111/idj.12630.

[2] Trindade D, Carvalho R, Machado V, et al. Prevalence of periodontitis in dentate people between 2011 and 2020: a systematic review and meta-analysis of epidemiological studies [J]. J Clin Periodontol, 2023, 50(5): 604-626. doi: 10.1111/jcpe.13769.

[3] Chen MX, Zhong YJ, Dong QQ, et al. Global, regional, and national burden of severe periodontitis, 1990-2019: an analysis of the Global Burden of Disease Study 2019 [J]. J Clin Periodontol, 2021, 48(9): 1165-1188. doi: 10.1111/jcpe.13506.

[4] Liu H, Wu X, Gang N, et al. Macrophage functional phenotype can be consecutively and reversibly shifted to adapt to microenvironmental changes [J]. Int J Clin Exp Med, 2015, 8(2): 3044-3053.

[5] Viola A, Munari F, Sánchez-Rodríguez R, et al. The metabolic signature of macrophage responses [J]. Front Immunol, 2019, 10: 1462. doi: 10.3389/fimmu.2019.01462.

[6] Roca FJ, Whitworth LJ, Prag HA, et al. Tumor necrosis factor induces pathogenic mitochondrial ROS in tuberculosis through reverse electron transport [J]. Science, 2022, 376(6600): eabh2841. doi: 10.1126/science.abh2841.

[7] Stifel U, Wolfschmitt EM, Vogt J, et al. Glucocorticoids coordinate macrophage metabolism through the regulation of the tricarboxylic acid cycle [J]. Mol Metab, 2022, 57: 101424. doi: 10.1016/j.molmet.2021.101424.

[8] Jones N, Blagih J, Zani F, et al. Fructose reprogrammes glutamine-dependent oxidative metabolism to support LPS-induced inflammation [J]. Nat Commun, 2021, 12(1): 1209. doi: 10.1038/s41467-021-21461-4.

[9] Fageeh HN, Fageeh HI, Khan SS, et al. Gingival crevicular fluid infiltrating CD14+ monocytes promote inflammation in periodontitis [J]. Saudi J Biol Sci, 2021, 28(5): 3069-3075. doi: 10.1016/j.sjbs.2021.02.049.

[10] 李小英, 李倩, 崔博淼, 等. 慢性牙周炎患者唾液诱导巨噬细胞分化和活化的研究[J]. 华西口腔医学杂志, 2018, 36(5): 508-513. doi: 10.7518/hxkq.2018.05.009.
Li XY, Li Q, Cui BM, et al. Saliva of periodontitis patients promotes macrophage differentiation and activation [J]. Hua Xi Kou Qiang Yi Xue Za Zhi, 2018, 36(5): 508-513. doi: 10.7518/hxkq.

2018.05.009.

[11] Li S, Hua Y, Liao C. Weakening of M1 macrophage and bone resorption in periodontitis cystathionine γ-lyase-deficient mice [J]. Oral Dis, 2024, 30(2): 769-779. doi: 10.1111/odi.14374.

[12] Almubarak A, Tanagala KKK, Papapanou PN, et al. Disruption of monocyte and macrophage homeostasis in periodontitis [J]. Front Immunol, 2020, 11: 330. doi: 10.3389/fimmu.2020.00330.

[13] Miao Y, He L, Qi X, et al. Injecting immunosuppressive M2 macrophages alleviates the symptoms of periodontitis in mice [J]. Front Mol Biosci, 2020, 7: 603817. doi: 10.3389/fmolb. 2020. 603817.

[14] Golub LM, Lee HM. Periodontal therapeutics: current host-modulation agents and future directions [J]. Periodontol 2000, 2020, 82 (1): 186-204. doi: 10.1111/prd.12315.

[15] Ni C, Zhou J, Kong N, et al. Gold nanoparticles modulate the crosstalk between macrophages and periodontal ligament cells for periodontitis treatment [J]. Biomaterials, 2019, 206: 115-132. doi: 10.1016/j.biomaterials.2019.03.039.

[16] Huangfu H, Du S, Zhang H, et al. Facile engineering of resveratrol nanoparticles loaded with 20(S)-protopanaxadiol for the treatment of periodontitis by regulating the macrophage phenotype [J]. Nanoscale. 2023, 15(17): 7894-7908. doi: 10.1039/d2nr06452a.

[17] Su Y, Ai S, Shen Y, et al. Regulatory effects of three-dimensional cultured lipopolysaccharide-pretreated periodontal ligament stem cell-derived secretome on macrophages [J]. Int J Mol Sci, 2023, 24 (8): 6981. doi: 10.3390/ijms24086981.

[18] Tian T, Chen L, Wang Z, et al. Sema3A drives alternative macrophage activation in the resolution of periodontitis via PI3K/AKT/mTOR signaling [J]. Inflammation, 2023, 46(3): 876 - 891. doi: 10.1007/s10753-022-01777-z.

[19] Li J, Liu Y, Lai W, et al. MicroRNA-126 regulates macrophage polarization to prevent the resorption of alveolar bone in diabetic periodontitis [J]. Arch Oral Biol, 2023, 150: 105686. doi: 10.1016/j.archoralbio.2023.105686.

[20] Vijayan V, Pradhan P, Braud L, et al. Human and murine macrophages exhibit differential metabolic responses to lipopolysaccharide - a divergent role for glycolysis [J]. Redox Biol, 2019, 22: 101147. doi: 10.1016/j.redox.2019.101147.

[21] Gosselin D, Link VM, Romanoski CE, et al. Environment drives selection and function of enhancers controlling tissue - specific macrophage identities [J]. Cell, 2014, 159(6): 1327 - 1340. doi: 10.1016/j.cell.2014.11.023.

[22] Jorgensen I, Miao EA. Pyroptotic cell death defends against intracellular pathogens [J]. Immunol Rev, 2015, 265(1): 130-142. doi: 10.1111/imr.12287.

[23] Rocha FRG, Delitto AE, de Souza JAC, et al. Relevance of caspase-1 and Nlrp3 inflammasome on inflammatory bone resorption in a murine model of periodontitis [J]. Sci Rep, 2020, 10(1): 7823. doi: 10.1038/s41598-020-64685-y.

[24] Han XD, Chen HM, Li C. Effect of human periodontal ligament stem cell-derived extracellular vesicles on macrophage pyroptosis and periodontal inflammatory injury in periodontitis [J]. Cells Tissues Organs, 2022, 211(1): 57-72. doi: 10.1159/000519569.

[25] Bostanci N, Emingil G, Saygan B, et al. Expression and regulation of the NALP3 inflammasome complex in periodontal diseases [J]. Clin Exp Immunol, 2009, 157(3): 415-422. doi: 10.1111/j.1365-2249.2009.03972.x.

[26] Yamaguchi Y, Kurita-Ochiai T, Kobayashi R, et al. Regulation of the NLRP3 inflammasome in *Porphyromonas gingivalis*-accelerated periodontal disease [J]. Inflamm Res, 2017, 66(1): 59-65. doi: 10.1007/s00011-016-0992-4.

[27] Ding PH, Yang MX, Wang NN, et al. *Porphyromonas gingivalis*-induced NLRP3 inflammasome activation and its downstream interleukin-1β release depend on caspase-4 [J]. Front Microbiol, 2020, 11: 1881. doi: 10.3389/fmicb.2020.01881.

[28] Chen Q, Liu X, Wang D, et al. Periodontal inflammation-triggered by periodontal ligament stem cell pyroptosis exacerbates periodontitis [J]. Front Cell Dev Biol, 2021, 9: 663037. doi: 10.3389/fcell.2021.663037.

[29] Zhang B, Yang Y, Yi J, et al. Hyperglycemia modulates M1/M2 macrophage polarization via reactive oxygen species overproduction in ligature-induced periodontitis [J]. J Periodontal Res, 2021, 56(5): 991-1005. doi: 10.1111/jre.12912.

[30] Zhou X, Wang Q, Nie L, et al. Metformin ameliorates the NLPP3 inflammasome mediated pyroptosis by inhibiting the expression of NEK7 in diabetic periodontitis [J]. Arch Oral Biol, 2020, 116: 104763. doi: 10.1016/j.archoralbio.2020.104763.

[31] Zhao P, Yue Z, Nie L, et al. Hyperglycaemia-associated macrophage pyroptosis accelerates periodontal inflamm-aging [J]. J Clin Periodontol, 2021, 48(10): 1379-1392. doi: 10.1111/jcpe.13517.

[32] Zhao Z, Ming Y, Li X, et al. Hyperglycemia aggravates periodontitis via autophagy impairment and ROS-inflammasome-mediated macrophage pyroptosis [J]. Int J Mol Sci, 2023, 24(7): 6309. doi: 10.3390/ijms24076309.

[33] Cheng R, Liu W, Zhang R, et al. *Porphyromonas gingivalis*-derived lipopolysaccharide combines hypoxia to induce caspase-1 activation in periodontitis [J]. Front Cell Infect Microbiol, 2017, 7: 474. doi: 10.3389/fcimb.2017.00474.

[34] Shao YX, Gong Q, Qi XM, et al. Paeoniflorin ameliorates macrophage infiltration and activation by inhibiting the TLR4 signaling pathway in diabetic nephropathy [J]. Front Pharmacol, 2019, 10: 566. doi: 10.3389/fphar.2019.00566.

[35] Montenegro Raudales JL, Yoshimura A, Sm Z, et al. Dental *Calculus* stimulates interleukin-1β secretion by activating NLRP3 inflammasome in human and mouse phagocytes [J]. PLoS One, 2016, 11(9): e0162865. doi: 10.1371/journal.pone.0162865.

[36] Gerlach B D, Ampomah P B, Yurdagul A, Jr., et al. Efferocytosis induces macrophage proliferation to help resolve tissue injury [J]. Cell Metab, 2021, 33(12): 2445 - 63. e8. doi: 10.1016/j.cmet.2021.10.015.

[37] Mehrotra P, Ravichandran KS. Drugging the efferocytosis process: concepts and opportunities [J]. Nat Rev Drug Discov, 2022, 21(8): 601-620. doi: 10.1038/s41573-022-00470-y.

[38] Zhang S, Weinberg S, DeBerge M, et al. Efferocytosis fuels re-

quirements of fatty acid oxidation and the electron transport chain to polarize macrophages for tissue repair [J]. Cell Metab, 2019, 29 (2): 443-456.e5. doi: 10.1016/j.cmet.2018.12.004.

[39] Yurdagul A, Jr., Subramanian M, Wang X, et al. Macrophage metabolism of apoptotic cell-derived arginine promotes continual efferocytosis and resolution of injury [J]. Cell Metab, 2020, 31(3): 518-33.e10. doi: 10.1016/j.cmet.2020.01.001.

[40] Schilperoort M, Ngai D, Katerelos M, et al. PFKFB2-mediated glycolysis promotes lactate-driven continual efferocytosis by macrophages [J]. Nat Metab, 2023, 5(3): 431-444. doi: 10.1038/s42255-023-00736-8.

[41] Zhang D, Tang Z, Huang H, et al. Metabolic regulation of gene expression by histone lactylation [J]. Nature, 2019, 574(7779): 575-580. doi: 10.1038/s41586-019-1678-1.

[42] Doran AC, Yurdagul A, Tabas I. Efferocytosis in health and disease [J]. Nat Rev Immunol, 2020, 20(4): 254-267. doi: 10.1038/s41577-019-0240-6.

[43] Nawaz Tipu H, Raza R, Jaffar S, et al. β2 Integrin Gene (ITGB2) mutation spectra in Pakistani families with leukocyte adhesion deficiency type 1 (LAD1) [J]. Immunobiology, 2020, 225(3): 151938. doi: 10.1016/j.imbio.2020.151938.

[44] Kajikawa T, Wang B, Li X, et al. Frontline science: activation of metabolic nuclear receptors restores periodontal tissue homeostasis in mice with leukocyte adhesion deficiency-1 [J]. J Leukoc Biol, 2020, 108(5): 1501-1514. doi: 10.1002/JLB.5HI0420-648R.

[45] Marchesan JT, Jiao Y, Moss K, et al. Common polymorphisms in IFI16 and AIM2 genes are associated with periodontal disease [J]. J Periodontol, 2017, 88(7): 663-672. doi: 10.1902/jop.2017.160553.

[46] Swanson KV, Girnary M, Alves T, et al. Interferon activated gene 204 protects against bone loss in experimental periodontitis [J]. J Periodontol, 2022, 93(9): 1366-1377. doi: 10.1002/JPER.21-0668.

[47] Cekici A, Sahinkaya S, Donmez MF, et al. Sirtuin6 and lipoxin A4 levels are decreased in severe periodontitis [J]. Clin Oral Investig, 2023, 27(12): 7407-7415. doi: 10.1007/s00784-023-05330-6.

[48] Godson C, Mitchell S, Harvey K, et al. Cutting edge: lipoxins rapidly stimulate nonphlogistic phagocytosis of apoptotic neutrophils by monocyte-derived macrophages [J]. J Immunol, 2000, 164(4): 1663-1667. doi: 10.4049/jimmunol.164.4.1663.

[49] Stańdo M, Piatek P, Namiecinska M, et al. Omega-3 polyunsaturated fatty acids EPA and DHA as an adjunct to non-surgical treatment of periodontitis: a randomized clinical trial [J]. Nutrients, 2020, 12(9): 2614. doi: 10.3390/nu12092614.

[50] Souza PR, Marques RM, Gomez EA, et al. Enriched marine oil supplements increase peripheral blood specialized pro-resolving mediators concentrations and reprogram host immune responses: a randomized double-blind placebo-controlled study [J]. Circ Res, 2020, 126(1): 75-90. doi: 10.1161/CIRCRESAHA.119.315506.

[51] Mizraji G, Heyman O, Van Dyke TE, et al. Resolvin D2 restrains Th1 immunity and prevents alveolar bone loss in murine periodontitis [J]. Front Immunol, 2018, 9: 785. doi: 10.3389/fimmu.2018.00785.

[52] Hong C, Kidani Y, A-Gonzalez N, et al. Coordinate regulation of neutrophil homeostasis by liver X receptors in mice [J]. J Clin Invest, 2012, 122(1): 337-347. doi: 10.1172/JCI58393.

[53] Fernandez-Boyanapalli RF, Falcone EL, Zerbe CS, et al. Impaired efferocytosis in human chronic granulomatous disease is reversed by pioglitazone treatment [J]. J Allergy Clin Immunol, 2015, 136 (5): 1399-1401.e3. doi: 10.1016/j.jaci.2015.07.034.

[54] Zhao J, Geng W, Wan K, et al. Lipoxin A4 promotes autophagy and inhibits overactivation of macrophage inflammasome activity induced by *Pg* LPS [J]. J Int Med Res, 2021, 49(2): 30006052098 1259. doi: 10.1177/0300060520981259.

[55] Wang CW, Yu SH, Fretwurst T, et al. Maresin 1 promotes wound healing and socket bone regeneration for alveolar ridge preservation [J]. J Dent Res, 2020, 99(8): 930-937. doi: 10.1177/0022034520917903.

（编辑　罗燕鸿）

官网