[DOI]10.12016/j.issn.2096-1456.202440305

·综述·

间充质干细胞外泌体对牙周炎中辅助性T细胞的调控作用

温雨琪，　郭淑娟，　丁一
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　口腔医学+前沿医学创新中心　四川大学华西口腔医院牙周科，四川　成都（610041）

【摘要】 辅助性T细胞（T helper cells，Th细胞）在牙周炎的发病机制中具有重要作用。在牙周炎的发生发展中，Th1细胞与Th17细胞及其分泌的致炎性细胞因子INF-γ、IL-17等水平上升，Th2细胞与调节性T细胞（regulatory T Cells，Tregs）及其产生的抑炎性细胞因子IL-4、TGF-β等水平降低。通过间充质干细胞（mesenchymal stem cells，MSCs）或其外泌体（exosomes，Exos）对牙周炎施加干预时，能够改变辅助性T细胞及相应细胞因子的变化趋势，从而减少牙周炎骨丧失或促进骨再生。间充质干细胞外泌体（mesenchymal stem cell-derived exosomes，MSC-exos）能够通过携带的蛋白分子及微RNAs直接调控辅助性T细胞。当前研究中发现MSC-exos可携带具有免疫抑制作用的蛋白分子：细胞程序性死亡配体1（programmed cell death 1-ligand，PD-L1）与吲哚胺-2，3-双加氧酶分子可调控Th17-Treg平衡；转化生长因子-β（transforming growth factor β，TGF-β）抑制T淋巴细胞增殖并通过维持叉头框P3（forkhead box protein O3，FOXP3）和Smad的表达促进Tregs分化；CD73则催化单磷酸腺苷分解产生腺苷，与Th1细胞内的腺苷2A受体结合，促使Th1细胞自身凋亡。MiRNA同样具有免疫调控能力：牙周膜干细胞外泌体携带的miRNA-155-5p通过靶向sirtuin-1而降低Th17细胞的分化，其携带的miR-205-5p能够靶向XBP1，进而恢复大鼠牙周炎局部的Th17-Treg平衡。牙髓干细胞外泌体通过miR-1246/Nfat5轴恢复Th17-Treg平衡；骨髓间充质干细胞外泌体携带的miR-1246靶向ACE2，使共培养的CD4阳性T淋巴细胞向Tregs分化。此外，MSC-exos也可以通过抗原呈递细胞或巨噬细胞等其他免疫细胞而间接促进Tregs的分化。本文主要针对辅助性T细胞在牙周炎中的变化及作用，以及间充质干细胞外泌体对辅助性T细胞的调控作用做一综述，希望为牙周炎的免疫治疗提供新思路。

【关键词】 牙周炎；　辅助性T细胞；　细胞因子；　转录因子；　间充质干细胞；　外泌体；　免疫调节；　微小RNAs
【中图分类号】 R78　**【文献标志码】** A　**【文章编号】** 2096-1456（2025）05-0409-08
【引用著录格式】 温雨琪，郭淑娟，丁一. 间充质干细胞外泌体对牙周炎中辅助性T细胞的调控作用[J]. 口腔疾病防治, 2025, 33(5): 409-416. doi:10.12016/j.issn.2096-1456.202440305.

微信公众号

Regulation of mesenchymal stem cell-derived exosomes on helper T cells in periodontitis

WEN Yuqi, GUO Shujuan, DING Yi.　State Key Laboratory of Oral Diseases & National Center for Stomatology & National Clinical Research Center for Oral Diseases & Frontier Innovation Center for Dental Medcine Plus & Department of Periodontics, West China Hospital of Stomatology, Sichuan University, Chengdu 610041, China
Corresponding author: DING Yi, Email: yiding2000@126.com, Tel: 86-28-85502343

【Abstract】 T helper cells (Th cells) play an important role in periodontitis. During the progression of periodontitis, the levels of pro-inflammatory cytokines such as INF-γ and IL-17, which are produced by Th1 and Th17 cells, are elevated, while the levels of anti-inflammatory cytokines such as IL-4 and TGF-β, which are secreted by Th2 cells and regulatory T cells (Tregs), are diminished. Interventions using mesenchymal stem cells (MSCs) or their exosomes can alter

【收稿日期】 2024-08-18；**【修回日期】** 2024-10-09
【基金项目】 国家自然科学基金项目（82071121）
【作者简介】 温雨琪，硕士研究生，Email：wyq23333@foxmail.com
【通信作者】 丁一，教授，博士，Email：yiding2000@126.com，Tel：86-28-85502343

the dynamics of helper T cell populations and their associated cytokine profiles, thereby mitigating the bone loss associated with periodontitis or even promoting bone regeneration. Mesenchymal stem cell-derived exosomes (MSC-exos) have been shown to directly modulate Th cell activity through the proteins and microRNAs they transport. Recent studies indicate that MSC-exos carry immune-suppressive protein molecules: PD-L1 and IDO contribute to regulating the balance between Th17 and Tregs; TGF-β inhibits the proliferation of T lymphocytes while facilitating differentiation into Tregs by sustaining forkhead box protein O3 (FOXP3) and Smad expression; and CD73 catalyzes the conversion of monophosphate adenosine into adenosine, which interacts with A2A receptors on Th1 cells to induce apoptosis in Th1 cells. In addition, microRNAs exhibit immunoregulatory functions: periodontal ligament stem cell-derived exosomes contain miRNA-155-5p, which targets sirtuin-1 to suppress Th17 cell differentiation. Furthermore, evidence in rat models of periodontitis suggests that these exosomes may also carry miR-205-5p targeting XBP1 to restore the balance between Th17 and Tregs. Dental pulp stem cell-derived exosomes reestablish this balance via the miR-1246/Nfat5 axis. Bone marrow mesenchymal stem cell-derived exosomes harbor miR-1246, which targets ACE2 to promote differentiation towards Tregs. Moreover, MSC-exos can indirectly enhance the differentiation of Tregs through interactions with other immune entities, such as antigen-presenting cells or macrophages. This article reviews the changes and roles of helper T cells in periodontitis, as well as the regulatory role of exosomes on helper T cells, hoping to provide new ideas for immunotherapy in the treatment of periodontitis.

【Key words】 periodontitis; T helper cells; cytokines; transcription factors; mesenchymal stem cells; exosomes; immunomodulation; microRNAs

J Prev Treat Stomatol Dis, 2025, 33(5): 409-416.

【Competing interests】 The authors declare no competing interests.

This study was supported by the grants from National Natural Science Foundation of China (No. 82071121).

1　宿主免疫失衡对牙周炎的影响

牙周炎是牙周组织对牙周微生物群的免疫失衡的结果，既存在牙周微生物群失调，也存在宿主免疫防御反应失衡[1]。牙周炎中的微生物失调表现为兼性需氧菌减少，致病性的厌氧菌属增多。这些致病性的微生物群具有更高的毒力，它们构成的菌斑生物膜也提高了菌群在炎症环境中生存繁殖的能力，促进微生物群的生态失调[2]。微生物失调本身并不一定导致牙周炎，宿主的免疫防御反应失衡是牙周炎发生发展的关键因素[3]。牙周炎的发病机制涉及复杂的免疫炎症级联反应，免疫炎症反应控制着患者的易感性，并受环境因素的影响[4]。先天性免疫反应及获得性免疫反应伴随牙周炎的始终。作为一种慢性炎症性疾病，获得性免疫反应在牙周炎的发展机制中具有重要作用，而辅助性T细胞是获得性免疫中的重要组成部分[5]。T淋巴细胞根据细胞表面标志分子的表达被划分为CD4阳性T淋巴细胞和CD8阳性T淋巴细胞，CD8阳性T淋巴细胞作为细胞杀伤T细胞介导细胞免疫，而CD4阳性T淋巴细胞大多作为辅助性T细胞通过分泌细胞因子参与细胞免疫及体液免疫之中[6]。在牙周炎中检测到辅助性T细胞及其分泌细胞因子的变化，而牙周炎的进展被控制时，能够检测到它们发生相反的变化。

2　Th细胞在牙周炎中的变化

2.1　Th细胞的分化、分型及功能

Th细胞是获得性免疫系统的关键参与者，由幼稚的CD4阳性T淋巴细胞在局部细胞因子和转录因子的调控下继续分化而来，包括辅助性T细胞1（T helper 1 cells，Th1细胞）、辅助性T细胞2（T helper 2 cells，Th2细胞）、辅助性T细胞17（T helper 17 cells，Th17细胞）、调节性T细胞（regulatory T cells，Tregs）等，在宿主的免疫防御以及炎症疾病中发挥重要作用[7]。

白细胞介素（interleukin，IL）和γ-干扰素（interferon-γ，IFN-γ）激活CD4阳性T淋巴细胞的转录因子，包括STAT1、STAT4和T-bet，促使其向Th1细胞分化[8]。IL-2和IL-4通过增加转录因子STAT6和GATA3的表达促进Th2细胞的分化[9]。Th1细胞的特征是高表达致炎性的INF-γ，从而激活巨噬细胞和CD8阳性T淋巴细胞等以清除细胞内病原体；Th2细胞大量产生IL-4，是宿主防御细胞外病原体和促进B细胞产生抗体的关键。INF-γ与IL-4分别对Th1细胞与Th2细胞具有正反馈的放大作用，进一步促进各自T细胞亚群的分化。此外，INF-γ和

IL-4在表达与功能上相互拮抗，因此Th1细胞和Th2细胞的发展也被认为是相互拮抗的，它们之间的关系被称为Th1-Th2平衡[10]。

Th17细胞的主要转录因子是孤儿核受体ROR-γT，它与信号转导与转录激活子（signal transducer and activator of tran-ions，STAT）等转录因子协同作用促使Th17细胞的分化[11]。Th17细胞具有促炎作用，表达IL-17、IL-22、粒细胞巨噬细胞集落刺激因子（granulocyte - macrophage colony - stimulating factor，GM-CSF）和IL-23R等分子[12]。IL-17能够与IL-1β等炎症因子协同作用，也可以招募炎症细胞。IL-17可上调趋化因子配体（CXCL）、CCL20、IL-1β、金属基质蛋白酶（matrix metallo proteinase，MMP）、PGE2以及GM-CSF的表达，促进吞噬细胞及中性粒细胞进入组织，加重组织破坏[13]。IL-17/ IL-23轴也可激活核因子κ-B配体受体致活剂（receptor activator ofnuclear factor kappa-B ligand，RANKL）信号导致牙槽骨吸收[14]。

Tregs和Th17细胞也存在拮抗作用。Tregs的转录因子包括叉头框P3（forkhead box protein O3，FOXP3）和STAT6。FOXP3通过STAT6诱导Tregs分化，它也是ROR-γT的负调节因子，能够下调Th17细胞水平[15]。Tregs通过表达细胞毒性T淋巴细胞相关抗原-4或分泌细胞因子发挥免疫抑制作用[16]。TGF-β与IL-10是Tregs表达的两种主要细胞因子，二者均能以自分泌的方式作用于Tregs，从而进一步促进TGF-β与IL-10的生成。TGF-β可以通过FOXP3信号诱导Tregs分化发育，也可能直接参与抑制效应T细胞[17]。IL-10具有抑制免疫炎症反应的作用，它与多种免疫细胞中的IL-10R结合后上调程序性死亡-配体1（programmed cell death 1 ligand 1，PD-L1）的表达，通过PD-L1/PD-1轴减弱了CD8阳性T淋巴细胞的细胞毒性[18]。

2.2　Th细胞及其细胞因子在牙周炎环境中的变化与作用

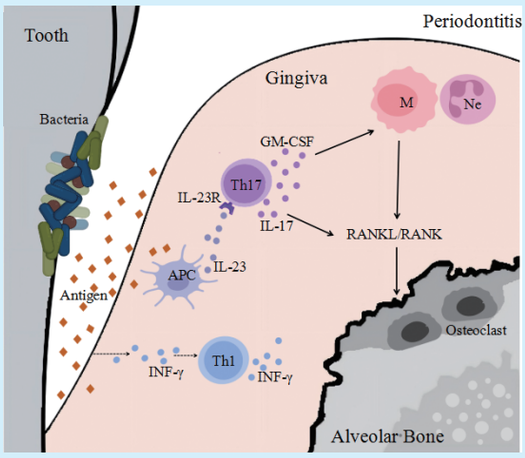
T淋巴细胞是口腔黏膜环境中最主要的免疫细胞群之一，Th细胞与牙周炎密切相关，但它们在牙周炎中的作用仍有争议。早期在人类和小鼠中进行的一些研究发现Th1细胞及其细胞因子表征于牙周炎初期，而Th2细胞在牙周炎进展后期占主要地位[19]。随后在关于牙周炎的一系列研究中发现，Th1细胞及INF-γ在牙周炎中升高，与之相对的是Th2细胞及IL-4下降[20]。这些研究的矛盾之处表明传统的Th1-Th2平衡不能完全解释牙周炎发生发展的机制，而Th17-Treg平衡极大地补充了Th细胞在牙周炎中的作用。近来的研究表明，牙周炎中Th1细胞、Th17细胞水平升高，Th2细胞、Tregs水平降低[21]。

Dutzan等[22]的研究表明，与野生型相比，Th17细胞分化缺陷的小鼠其牙槽骨吸收程度显著降低。大鼠牙周炎中的研究证实，抑制STAT3等Th17细胞转录因子的表达，能够减少牙周炎中的骨破坏[23]。Tregs的作用与免疫抑制有关，Tregs可在整个牙周炎过程中释放抗炎细胞因子转化生长因子-β（transforming growth factor-β，TGF-β）和IL-10，参与牙周炎症和牙周骨稳态[24]。

Th17细胞和Tregs是一组互相拮抗的细胞，它们的相互关系被称为Th17-Treg平衡。Th17-Treg失衡可能是牙周炎发病的关键[25]。牙龈卟啉单胞菌优先刺激Th17细胞分化，Tregs的关键转录因子FOXP3的基因表达降低，破坏Th17-Treg平衡[26]。皮下接种牙龈卟啉单胞菌的疫苗则可以降低小鼠颈部淋巴结及外周血中Th17细胞及IL-17的水平，增加Tregs、IL-10和TGF-β的生成，从而降低小鼠牙周炎中的组织破坏[27]。现有研究表明，Th17-Treg细胞平衡调节牙周RANKL/骨保护素（osteoprotegerin，OPG）的表达，从而影响牙周骨代谢[28]。活化的Th17细胞可增强RANKL的表达，激活RANKL/RANK信号通路，促进炎症性骨吸收。而Th1细胞、Th2细胞和Tregs抑制或弱促进RANKL的表达。因此，Tregs浸润增加可能表明牙周组织的破坏被抑制，但Tregs在牙周炎晚期功能失调，转化为Th17细胞，进一步促进Th17细胞驱动的牙周炎骨丧失[29]（图1）。

3　间充质干细胞外泌体对Th细胞的免疫调节作用

间充质干细胞（mesenchymal stem cell，MSCs）是一种具有自我更新能力和多向分化能力的细胞，具有优秀的免疫调节能力与组织再生潜能，已被作为各种组织工程应用的潜在候选细胞。在牙周炎治疗的研究中发现，MSCs能够改变牙周炎中辅助性T细胞及其细胞因子[30]。MSCs主要通过旁分泌作用及细胞间直接信息交流来发挥其免疫调节功能，其中外泌体（exosomes，Exos）是MSCs旁分泌因子中的一种，能够发挥与其亲本干细胞类似的免疫调节功能[31]。Exos是一种细胞外囊泡，具有双层膜结构，通过质膜内陷或细胞内含有腔内囊泡的多泡体形成而产生，其直径范围40～160 nm，



The IL-23R on the membrane surface of Th17 cells binds to IL-23 secreted by antigen-presenting cells, promotes the secretion of cytokines such as IL-17 and GM-CSF, which aggravates alveolar bone destruction. Stimulated by bacterial pathogens, INF-γ levels in the gingiva increase, promoting Th1 cell differentiation and further production of INF-γ. CSF: colony-stimulating factor. APC: antigen-presenting cells. M: macrophages. Ne: neutrophils. GM-CSF: granulocyte-macrophage. IFN-γ:interferon-γ

Figure 1　Th1 cells and Th17 cells aggravate periodontal tissue destruction

图1　Th1细胞与Th17细胞加重牙周组织破坏

含有复杂而丰富的蛋白质、核酸、脂质、氨基酸和代谢物，这些成分可以反映Exos的细胞来源[32]，当前研究集中在Exos携带的蛋白质与核酸在功能中的作用[33]。间充质干细胞外泌体（MSC-exos）通过调节免疫相关通路[34]或携带与免疫调节相关的蛋白分子与免疫效应细胞相互作用，调节T细胞的增殖、活化、迁移、分化和凋亡。

3.1　MSC-exos对Th细胞具有免疫抑制作用

MSC-exos抑制CD4阳性T淋巴细胞的增殖与活化，抑制其向病灶区的迁移。Dadgar等[35]的研究表明从健康人肠系膜中分离得到的MSC-exos能够抑制CD4阳性T淋巴细胞增殖，使其维持未活化的状态，从而减轻葡聚糖硫酸钠诱导的结肠炎。Zheng等[36]发现人牙周膜干细胞外泌体能够抑制CD4阳性T淋巴细胞在病灶中的浸润，从而降低牙周炎的损伤。

在慢性炎症性疾病的研究中，MSC-exos通过调控CD4阳性T淋巴细胞分化实现免疫抑制，减轻炎症反应。在类风湿性关节炎的多项研究中发现MSC-exos能够降低视黄醇相关孤儿受体γ-t（retinoid-related orphan receptor gamma t，RORγt）和STAT3的表达[37]，从而促进活化的CD4阳性T淋巴细胞向Tregs分化，抑制其向Th17细胞、Th1细胞分化[38]，下调IL-17、INF-γ、TNF-α水平，上调TGF-β、IL-10水平[36, 39]。MSC-exos也能够使Th1细胞向Th2细胞转化，IL-4表达量增加，在细胞水平及细胞因子分泌水平上恢复Th1-Th2平衡，从而减轻结肠炎[40]。在牙周炎动物模型中，牙龈来源的间充质干细胞外泌体有效地促进单核细胞中抗炎性细胞因子IL-10与抗炎表型特征标志物Arg-1和CD206的表达，同时抑制TNF-α的表达。还发现牙龈来源的间充质干细胞外泌体通过抑制CD4阳性T淋巴细胞活化、促进Tregs形成和抑制IFN-γ产生来影响Th细胞的功能，进一步的大鼠牙周炎模型也证实了其治疗牙周炎的有效性[41-43]。Liu等[44]研究发现骨髓间充质干细胞外泌体作用于牙周炎大鼠后，牙周膜中TGF-β表达量增加，牙周骨再生作用显著。

另外，MSC-exos也能够通过调节辅助性T细胞的凋亡发挥免疫抑制作用。在人-鼠异种慢性移植物抗宿主病模型中，致病的Th1细胞与Th17细胞显著增加，人骨髓间充质干细胞外泌体后能够促使Th1细胞凋亡[45]、阻断Th17细胞分化[46]，而Tregs增加，进而缓解全身炎症反应，逆转了该疾病模型的致死性结局。总体而言，MSC-exos通过抑制CD4阳性T淋巴细胞的增殖活化、促进Tregs分化以及促进CD4阳性T淋巴细胞的凋亡发挥免疫抑制作用，但在牙周炎疾病中，MSC-exos抑制T淋巴细胞增殖及促进其凋亡的研究较少。

3.2　MSC-exos对Th细胞的免疫抑制机制

MSC-exos可以通过携带的蛋白质和miRNA调节免疫相关的通路，从而直接调控Th细胞功能，也可以通过调控抗原呈递细胞（antigen-presenting cells，APCs）等免疫细胞而间接调控Th细胞（图2）。

3.2.1　MSC-exos对Th细胞的直接调控作用

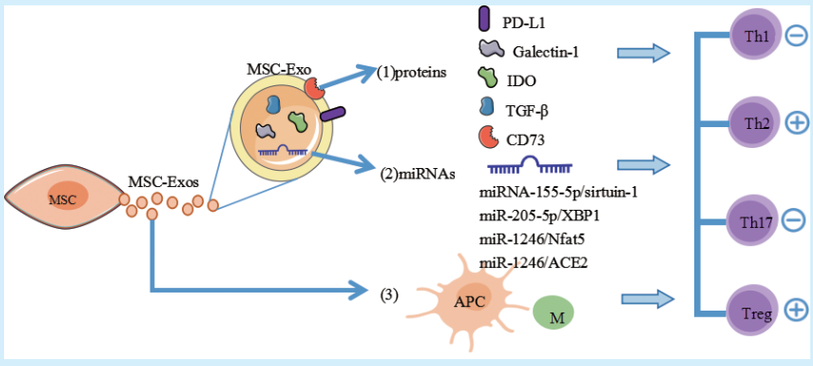
MSC-exos能够携带PD-L1、TGF-β、IDO和CD73等分子[47]，这些蛋白分子具有免疫抑制作用。PD-L1通过与T细胞表面的PD-1结合促进活化T淋巴细胞的凋亡，还可以促进Tregs分化[48]。沉默PD-L1的小鼠模型证明，PD-L1自身调控Tregs的发育，并增加FOXP3的表达以及维持Tregs水平[49]。在一项结肠炎的研究中发现，MSC-exos携带的PD-L1通过PTEN/PI3K/AKT/mTOR轴调节Th17-Treg平衡，使得Th17细胞及IL-17水平降低，而Tregs与TGF-β水平升高[50]。TGF-β能够抑制T淋巴细胞增殖，也可以

通过维持FOXP3和SMAD的表达促使幼稚的CD4阳性T淋巴细胞或Th17细胞向Tregs分化[51]。IDO是一种双加氧酶，研究发现具有较高IDO含量的MSC-exos可以抑制Th17细胞、促进Tregs分化，调控Th17-Treg细胞平衡[52]。MSC-exos膜表面的CD73具有单磷酸腺苷（AMP）酶活性，催化活化T细胞中的大量AMP分解产生腺苷，Th1细胞内存在腺苷2A受体，与腺苷结合促进自身凋亡，从而降低TNF-α和IFN-γ水平[45]。

MSC-exos携带的多种miRNA能够促进CD4阳性T淋巴细胞向Tregs等抗炎表型转化，发挥免疫抑制作用[47]。Zheng等[36]研究发现牙周膜干细胞外泌体携带的miRNA-155-5p通过靶向sirtuin-1而降低Th17细胞的分化，增加Tregs的分化及表达，从而调节慢性牙周炎的Th17-Treg平衡，Kang等[53]则发现牙周膜干细胞外泌体携带的miR-205-5p能够靶向XBP1，进而恢复大鼠牙周炎局部的Th17-Treg平衡。3D培养牙髓干细胞，其外泌体通过miR-1246/Nfat5轴恢复Th17-Treg平衡，比常规细胞培养方法提取的外泌体具有更好地减少牙周炎骨丧失的效果[54]。骨髓间充质干细胞外泌体也具有良好的免疫调节能力，其携带的miR-1246靶向ACE2，并提高CD4阳性T淋巴细胞中p-YAP1/YAP1比，使共培养的CD4阳性T淋巴细胞向Tregs分化，体内实验表明其能够恢复牙周炎小鼠外周血Th17-Treg平衡，并减轻牙周炎骨丧失[55]。INF-γ预处理骨髓间充质干细胞后，其外泌体中的miR125a及mi125b直接靶向STAT3，降低STAT3的表达，从而抑制Th17细胞分化，减轻小鼠结肠炎[56]。

3.2.2　MSC-exos对Th细胞的间接调控作用　MSC-exos可以通过巨噬细胞和APCs调控T细胞。经过MSC-exos预处理后的THP-1细胞可以诱导Tregs分化[57]。在CD4阳性T淋巴细胞和MSC-exos共培养体系中加入巨噬细胞可以更加抑制T细胞活化，并通过上调FOXP3的表达显著增加Tregs的比例[58]。

树状突细胞（dendritic cells，DCs）是一类抗原呈递细胞，被牙龈卟啉单胞菌激活的DCs可调控CD4阳性T淋巴细胞，促进Th17细胞分化，与牙槽骨破坏相关[59]。但MSC-exos与DCs共培养可形成免疫耐受型树突细胞（tolerogenic dendritic cells，tolDCs），tolDCs则对T细胞有抑制作用，能够上调Tregs水平[60]。Zhang等[57]观察到MSC-exos处理后的CD11C+的APCs激活CD4阳性T淋巴细胞时，能够将其极化为Tregs。因此，MSC-exos可以通过调控其他免疫细胞间接改变辅助性T细胞水平。



(1) MSC-exos are equipped with various proteins that are exert direct regulatory effects on Th cells. (2) The miRNAs contained within MSC-exos have the capacity to directly modulate Th cells. (3) MSC-exos indirectly influence Th cells through interactions with APCs and macrophages. MSC: mesenchymal stem cell. MSC-exos: mesenchymal stem cell-derived exosomes. miRNAs: microRNAs. APC: antigen-presenting cells. M: macrophages. Th cells: T helper cells. XBP1: X-box binding protein 1. Nfat5: nuclear factor of activated T cells 5. ACE2: angiotensin-converting enzyme 2. PD-L1: programmed cell death 1 ligand 1. TGF-β: transforming growth factor-β

Figure 2　Regulation of T helper cells by MSC-exos

图2　间充质干细胞外泌体对辅助性T细胞的调控

4　MSC-exos在牙周炎治疗中的应用潜能

传统的牙周治疗方式主要目的是尽可能清除牙石、菌斑生物膜和病变牙骨质，从而控制炎症，但促进牙周组织再生的效果不佳。近年来基于干细胞和免疫细胞的新技术在牙周炎中受到广泛关注，在多项研究中发现间充质干细胞能够通过调节Th细胞等参与牙周炎骨丧失及骨再生的过程[61-62]。Li等[63]在小鼠牙周炎模型中应用白藜芦醇促进牙周膜干细胞的功能，降低牙周炎位点处TNF-α$^+$ CD4$^+$炎性T淋巴细胞浸润水平，减少骨丧

失。但是，间充质干细胞具有一定的局限性，如干细胞扩增过程中去分化、移植后再生效率降低、移植后细胞表型不稳定、不同患者环境对免疫细胞表型的影响以及移植细胞的生产、运输、储存和安全标准不一致等。而MSC-exos作为间充质干细胞旁分泌因子中的一种，具有类似母本细胞的免疫调控能力，具有免疫清除率低、成瘤性低、储存容易、更有效地递送活性物质、穿透血脑屏障等狭窄空间的能力强等优点[32, 61]。因此，MSC-exos正在成为细胞疗法的一种替代方案。

目前MSC-exos的免疫调节作用及机制尚未完全清晰，不同来源的外泌体其作用也有所偏差[64]，在牙周炎中的研究集中在MSC-exos对Th17-Treg细胞平衡的影响。总的来说MSC-exos能够调节牙周炎中的Th细胞，从而减少牙周炎骨丧失，或促进骨再生。但如何提高MSC-exos的产量、如何控制MSC-exos的成分，以及MSC-exos更为具体的免疫调节机制与介入牙周炎治疗的方式和时机仍需要进一步研究。

【Author contributions】 Wen YQ wrote the article. Guo SJ revised the article. Ding Y conceptualized and reviewed the article. All authors read and approved the final manuscript as submitted.

参考文献

[1] Han N, Liu Y, Du J, et al. Regulation of the host immune microenvironment in periodontitis and periodontal bone remodeling[J]. Int J Mol Sci, 2023, 24(4): 3158. doi: 10.3390/ijms24043158.

[2] Iniesta M, Chamorro C, Ambrosio N, et al. Subgingival microbiome in periodontal health, gingivitis and different stages of periodontitis[J]. J Clin Periodontol, 2023, 50(7): 905 - 920. doi: 10.1111/jcpe.13793.

[3] Hajishengallis G, Chavakis T, Lambris JD. Current understanding of periodontal disease pathogenesis and targets for host-modulation therapy[J]. Periodontol 2000, 2020, 84(1): 14 - 34. doi: 10.1111/prd.12331.

[4] 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.

[5] Gaffen SL, Moutsopoulos NM. Regulation of host-microbe interactions at oral mucosal barriers by type 17 immunity[J]. Sci Immunol, 2020, 5(43): eaau4594. doi: 10.1126/sciimmunol.aau4594.

[6] Avery D, Morandini L, Sheakley L, et al. $CD4^+$ and $CD8^+$ T cells reduce inflammation and promote bone healing in response to titanium implants[J]. Acta Biomater, 2024, 179: 385 - 397. doi: 10.1016/j.actbio.2024.03.022.

[7] Zhu X, Zhu J. CD4 T helper cell subsets and related human immunological disorders[J]. Int J Mol Sci, 2020, 21(21): 8011. doi: 10.3390/ijms21218011.

[8] Tang YY, Wang DC, Chen YY, et al. Th1-related transcription factors and cytokines in systemic lupus erythematosus[J]. Front Immunol, 2023, 14: 1305590. doi: 10.3389/fimmu.2023.1305590.

[9] León B. A model of Th2 differentiation based on polarizing cytokine repression[J]. Trends Immunol, 2023, 44(6): 399 - 407. doi: 10.1016/j.it.2023.04.004.

[10] Ruterbusch M, Pruner KB, Shehata L, et al. *In vivo* $CD4^+$ T cell differentiation and function: revisiting the Th1/Th2 paradigm[J]. Annu Rev Immunol, 2020, 38: 705-725. doi: 10.1146/annurev-immunol-103019-085803.

[11] Mickael ME, Bhaumik S, Basu R. Retinoid-related orphan receptor RORγt in $CD4^+$ T-cell-mediated intestinal homeostasis and inflammation[J]. Am J Pathol, 2020, 190(10): 1984 - 1999. doi: 10.1016/j.ajpath.2020.07.010.

[12] Niu Y, Zhou Q. Th17 cells and their related cytokines: vital players in progression of malignant pleural effusion[J]. Cell Mol Life Sci, 2022, 79(4): 194. doi: 10.1007/s00018-022-04227-z.

[13] Kumar R, Theiss AL, Venuprasad K. RORγt protein modifications and IL-17-mediated inflammation[J]. Trends Immunol, 2021, 42(11): 1037-1050. doi: 10.1016/j.it.2021.09.005.

[14] Del Carmen Ruíz-Gutiérrez A, Rodríguez-Montaño R, Pita-López ML, et al. Inverse behavior of IL-23R and IL-17RA in chronic and aggressive periodontitis[J]. J Periodontal Implant Sci, 2021, 51(4): 254-263. doi: 10.5051/jpis.2005380269.

[15] Savage PA, Klawon DEJ, Miller CH. Regulatory T cell development[J]. Annu Rev Immunol, 2020, 38: 421-453. doi: 10.1146/annurev-immunol-100219-020937.

[16] Sakaguchi S, Mikami N, Wing JB, et al. Regulatory T cells and human disease[J]. Annu Rev Immunol, 2020, 38: 541 - 566. doi: 10.1146/annurev-immunol-042718-041717.

[17] Moreau JM, Velegraki M, Bolyard C, et al. Transforming growth factor-β1 in regulatory T cell biology[J]. Sci Immunol, 2022, 7(69): eabi4613. doi: 10.1126/sciimmunol.abi4613.

[18] Shiri AM, Zhang T, Bedke T, et al. IL-10 dampens antitumor immunity and promotes liver metastasis *via* PD-L1 induction[J]. J Hepatol, 2024, 80(4): 634-644. doi: 10.1016/j.jhep.2023.12.015.

[19] Garlet GP, Cardoso CR, Silva TA, et al. Cytokine pattern determines the progression of experimental periodontal disease induced by *Actinobacillus actinomycetemcomitans* through the modulation of MMPs, RANKL, and their physiological inhibitors[J]. Oral Microbiol Immunol, 2006, 21(1): 12 - 20. doi: 10.1111/j. 1399 - 302X.2005.00245.x.

[20] Gonzales JR, Gröger S, Boedeker RH, et al. Expression and secretion levels of Th1 and Th2 cytokines in patients with aggressive periodontitis[J]. Clin Oral Investig, 2012, 16(5): 1463-1473. doi: 10.1007/s00784-011-0634-8.

[21] Yuan Y, Zhang H, Gu Q, et al. Analysis of Th-cell subsets in local and systemic environments from experimental periodontitis rats[J]. Mol Oral Microbiol, 2023, 38(2): 83-92. doi: 10.1111/omi.12376.

[22] Dutzan N, Kajikawa T, Abusleme L, et al. A dysbiotic microbiome triggers T_H17 cells to mediate oral mucosal immunopathology in mice and humans[J]. Sci Transl Med, 2018, 10(463): eaat0797. doi: 10.1126/scitranslmed.aat0797.

[23] Qiao X, Tang J, Dou L, et al. Dental pulp stem cell-derived exosomes regulate anti-inflammatory and osteogenesis in periodontal ligament stem cells and promote the repair of experimental periodontitis in rats[J]. Int J Nanomedicine, 2023, 18: 4683-4703. doi: 10.2147/IJN.S420967.

[24] Zou J, Zeng Z, Xie W, et al. Immunotherapy with regulatory T and B cells in periodontitis[J]. Int Immunopharmacol, 2022, 109: 108797. doi: 10.1016/j.intimp.2022.108797.

[25] Cavalla F, Letra A, Silva RM, et al. Determinants of periodontal/periapical lesion stability and progression[J]. J Dent Res, 2021, 100(1): 29-36. doi: 10.1177/0022034520952341.

[26] Li M, Qu R, Li P, et al. Epimedium polysaccharides mitigates *Porphyromonas gingivalis*-exacerbated intestinal inflammation by suppressing the Th17 pathway and modulating the gut microbiota[J]. Int J Biol Macromol, 2024, 278(Pt 1): 134203. doi: 10.1016/j.ijbiomac.2024.134203.

[27] Wang L, Guan N, Jin Y, et al. Subcutaneous vaccination with *Porphyromonas gingivalis* ameliorates periodontitis by modulating Th17/Treg imbalance in a murine model[J]. Int Immunopharmacol, 2015, 25(1): 65-73. doi: 10.1016/j.intimp.2015.01.007.

[28] Cafferata EA, Castro-Saavedra S, Fuentes-Barros G, et al. Boldine inhibits the alveolar bone resorption during ligature-induced periodontitis by modulating the Th17/Treg imbalance[J]. J Periodontol, 2021, 92(1): 123-136. doi: 10.1002/JPER.20-0055.

[29] Bittner-Eddy PD, Fischer LA, Costalonga M. Transient expression of IL-17A in Foxp3 fate-tracked cells in *Porphyromonas gingivalis*-mediated oral dysbiosis[J]. Front Immunol, 2020, 11: 677. doi: 10.3389/fimmu.2020.00677.

[30] Li P, Ou Q, Shi S, et al. Immunomodulatory properties of mesenchymal stem cells/dental stem cells and their therapeutic applications[J]. Cell Mol Immunol, 2023, 20(6): 558-569. doi: 10.1038/s41423-023-00998-y.

[31] Lei F, Li M, Lin T, et al. Treatment of inflammatory bone loss in periodontitis by stem cell-derived exosomes[J]. Acta Biomater, 2022, 141: 333-343. doi: 10.1016/j.actbio.2021.12.035.

[32] Kalluri R, LeBleu VS. The biology, function, and biomedical applications of exosomes[J]. Science, 2020, 367(6478): eaau6977. doi: 10.1126/science.aau6977.

[33] Hassanzadeh A, Rahman HS, Markov A, et al. Mesenchymal stem/stromal cell-derived exosomes in regenerative medicine and cancer; overview of development, challenges, and opportunities[J]. Stem Cell Res Ther, 2021, 12(1): 297. doi: 10.1186/s13287-021-02378-7.

[34] 艾克帕尔·艾尔肯, 陈晓涛. 牙源性间充质干细胞来源的外泌体在牙周免疫调节的研究进展 [J]. 口腔疾病防治, 2024, 32(10): 814-820. doi: 10.12016/j.issn.2096-1456.202330506.
Akbar Arkin, Chen XT. Research progress on dental mesenchymal stem cell-derived exosomes in periodontal immune regulation[J]. J Prev Treat Stomatol Dis, 2024, 32(10): 814-820. doi: 10.12016/j.issn.2096-1456.202330506.

[35] Dadgar N, Altemus J, Li Y, et al. Effect of Crohn's disease mesenteric mesenchymal stem cells and their extracellular vesicles on T-cell immunosuppressive capacity[J]. J Cell Mol Med, 2022, 26(19): 4924-4939. doi: 10.1111/jcmm.17483.

[36] Zheng Y, Dong C, Yang J, et al. Exosomal microRNA-155-5p from PDLSCs regulated Th17/Treg balance by targeting sirtuin-1 in chronic periodontitis[J]. J Cell Physiol, 2019, 234(11): 20662-20674. doi: 10.1002/jcp.28671.

[37] Tavasolian F, Hosseini AZ, Soudi S, et al. MiRNA-146a improves immunomodulatory effects of MSC-derived exosomes in rheumatoid arthritis[J]. Curr Gene Ther, 2020, 20(4): 297-312. doi: 10.2174/1566523220666200916120708.

[38] Wang S, Huo J, Liu Y, et al. Impaired immunosuppressive effect of bone marrow mesenchymal stem cell-derived exosomes on T cells in aplastic anemia[J]. Stem Cell Res Ther, 2023, 14(1): 285. doi: 10.1186/s13287-023-03496-0.

[39] Samarpita S, Li X. Leveraging exosomes as the next-generation bio-shuttles: the next biggest approach against Th17 cell catastrophe [J]. Int J Mol Sci, 2023, 24(8): 7647. doi: 10.3390/ijms24087647.

[40] Guo G, Tan Z, Liu Y, et al. The therapeutic potential of stem cell-derived exosomes in the ulcerative colitis and colorectal cancer[J]. Stem Cell Res Ther, 2022, 13(1): 138. doi: 10.1186/s13287-022-02811-5.

[41] Zarubova J, Hasani-Sadrabadi MM, Dashtimoghadam E, et al. Engineered delivery of dental stem-cell-derived extracellular vesicles for periodontal tissue regeneration[J]. Adv Healthc Mater, 2022, 11(12): e2102593. doi: 10.1002/adhm.202102593.

[42] Zhang Y, Wang Z, Shi B, et al. Effect of gingival mesenchymal stem cell-derived exosomes on inflammatory macrophages in a high-lipid microenvironment[J]. Int Immunopharmacol, 2021, 94: 107455. doi: 10.1016/j.intimp.2021.107455.

[43] Wang R, Ji Q, Meng C, et al. Role of gingival mesenchymal stem cell exosomes in macrophage polarization under inflammatory conditions[J]. Int Immunopharmacol, 2020, 81: 106030. doi: 10.1016/j.intimp.2019.106030.

[44] Liu L, Guo S, Shi W, et al. Bone marrow mesenchymal stem cell-derived small extracellular vesicles promote periodontal regeneration[J]. Tissue Eng Part A, 2021, 27(13/14): 962-976. doi: 10.1089/ten.TEA.2020.0141.

[45] Amarnath S, Foley JE, Farthing DE, et al. Bone marrow-derived mesenchymal stromal cells harness purinergenic signaling to tolerize human Th1 cells *in vivo*[J]. Stem Cells, 2015, 33(4): 1200-1212. doi: 10.1002/stem.1934.

[46] Liu W, Zhou N, Liu Y, et al. Mesenchymal stem cell exosome-derived miR-223 alleviates acute graft-versus-host disease *via* reducing the migration of donor T cells[J]. Stem Cell Res Ther, 2021, 12(1): 153. doi: 10.1186/s13287-021-02159-2.

[47] Qian X, An N, Ren Y, et al. Immunosuppressive effects of mesenchymal stem cells-derived exosomes[J]. Stem Cell Rev Rep, 2021, 17(2): 411-427. doi: 10.1007/s12015-020-10040-7.

[48] Groeger S, Meyle J. The role of programmed death receptor(PD-)1/PD-ligand(L)1 in periodontitis and cancer[J]. Periodontol 2000, 2024, 96(1): 150-169. doi: 10.1111/prd.12548.

[49] Francisco LM, Salinas VH, Brown KE, et al. PD-L1 regulates the development, maintenance, and function of induced regulatory T cells[J]. J Exp Med, 2009, 206(13): 3015-3029. doi: 10.1084/jem.20090847.

[50] He H, Chen Q, Fan H, et al. Extracellular vesicles produced by bone marrow mesenchymal stem cells overexpressing programmed death-ligand 1 ameliorate dextran sodium sulfate-induced ulcerative colitis in rats by regulating Th17/Treg cell balance through PTEN/PI3K/AKT/mTOR axis[J]. J Gastroenterol Hepatol, 2022, 37(12): 2243-2254. doi: 10.1111/jgh.15987.

[51] Wang J, Zhao X, Wan YY. Intricacies of TGF-beta signaling in Treg and Th17 cell biology[J]. Cell Mol Immunol, 2023, 20(9), 1002-1022. doi: 10.1038/s41423-023-01036-7.

[52] Li XL, Li H, Zhang M, et al. Exosomes derived from atorvaSTATin-modified bone marrow dendritic cells ameliorate experimental autoimmune myasthenia gravis by up-regulated levels of IDO/Treg and partly dependent on FasL/Fas pathway[J]. J Neuroinflammation, 2016, 13: 8. doi: 10.1186/s12974-016-0475-0.

[53] Kang L, Miao Y, Jin Y, et al. Exosomal miR-205-5p derived from periodontal ligament stem cells attenuates the inflammation of chronic periodontitis *via* targeting XBP1[J]. Immun Inflamm Dis, 2023, 11(1): e743. doi: 10.1002/iid3.743.

[54] Zhang Y, Chen J, Fu H, et al. Exosomes derived from 3D-cultured MSCs improve therapeutic effects in periodontitis and experimental colitis and restore the Th17 cell/Treg balance in inflamed periodontium[J]. Int J Oral Sci, 2021, 13(1): 43. doi: 10.1038/s41368-021-00150-4.

[55] Xia Y, Cheng T, Zhang C, et al. Human bone marrow mesenchymal stem cell-derived extracellular vesicles restore Th17/Treg homeostasis in periodontitis *via* miR-1246[J]. FASEB J, 2023, 37(11): e23226. doi: 10.1096/fj.202300674RR.

[56] Yang R, Huang H, Cui S, et al. IFN-γ promoted exosomes from mesenchymal stem cells to attenuate colitis *via* miR-125a and miR-125b[J]. Cell Death Dis, 2020, 11(7): 603. doi: 10.1038/s41419-020-02788-0.

[57] Zhang B, Yeo RWY, Lai RC, et al. Mesenchymal stromal cell exosome-enhanced regulatory T-cell production through an antigen-presenting cell-mediated pathway[J]. Cytotherapy, 2018, 20(5): 687-696. doi: 10.1016/j.jcyt.2018.02.372.

[58] Heo JS, Choi Y, Kim HO. Adipose-derived mesenchymal stem cells promote M2 macrophage phenotype through exosomes[J]. Stem Cells Int, 2019, 2019: 7921760. doi: 10.1155/2019/7921760.

[59] El-Awady AR, Elashiry M, Morandini AC, et al. Dendritic cells a critical link to alveolar bone loss and systemic disease risk in periodontitis: immunotherapeutic implications[J]. Periodontol 2000, 2022, 89(1): 41-50. doi: 10.1111/prd.12428.

[60] Shahir M, Mahmoud Hashemi S, Asadirad A, et al. Effect of mesenchymal stem cell-derived exosomes on the induction of mouse tolerogenic dendritic cells[J]. J Cell Physiol, 2020, 235(10): 7043-7055. doi: 10.1002/jcp.29601.

[61] Huang X, Wang H, Wang C, et al. The applications and potentials of extracellular vesicles from different cell sources in periodontal regeneration[J]. Int J Mol Sci, 2023, 24(6): 5790. doi: 10.3390/ijms24065790.

[62] Paganelli A, Trubiani O, Diomede F, et al. Immunomodulating profile of dental mesenchymal stromal cells: a comprehensive overview[J]. Front Oral Health, 2021, 2: 635055. doi: 10.3389/froh.2021.635055.

[63] Li W, Huang X, Yu W, et al. Activation of functional somatic stem cells promotes endogenous tissue regeneration[J]. J Dent Res, 2022, 101(7): 802-811. doi: 10.1177/00220345211070222.

[64] Chen L, Zhu S, Guo S, et al. Mechanisms and clinical application potential of mesenchymal stem cells-derived extracellular vesicles in periodontal regeneration[J]. Stem Cell Res Ther, 2023, 14(1): 26. doi: 10.1186/s13287-023-03242-6.

（编辑　周春华）

官网