

[DOI] 10.12016/j.issn.2096-1456.202330506

· 综述 ·

# 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

阿克帕尔·艾尔肯<sup>1</sup>, 陈晓涛<sup>1,2</sup>

1. 新疆维吾尔自治区人民医院, 新疆维吾尔自治区 乌鲁木齐(830000); 2. 新疆维吾尔自治区人民医院口腔科, 新疆维吾尔自治区 乌鲁木齐(830000)

**【摘要】** 外泌体(exosomes, EXOs)是细胞间通讯的重要介质,其内含有多种物质,包括 miRNA、mRNA、DNA 和蛋白质等,可通过多种方式作用于靶细胞。外泌体作为“无细胞治疗”手段,具有广阔的医学应用前景。EXOs 的内含物随供体细胞及其状态的变化而变化,因此来自不同类型细胞的 EXOs 可能表现出不同的生物学效应。牙源性间充质干细胞(dental mesenchymal stem cells, DMSCs)来源的 EXOs 因其在组织再生医学和免疫调节领域表现出的生物学特性而受到越来越多的关注。在牙周免疫调节过程中促炎型(M1型)/抗炎型(M2型)巨噬细胞以及辅助性T细胞(Th17)/调节性T细胞(Treg)之间的平衡转化是研究热点。现有研究表明,牙源性间充质干细胞来源的外泌体 DMSCs-EXOs 能够促进巨噬细胞和T细胞的转化并且这种功能可能取决于周围微环境以及干细胞的组织来源等因素,如牙髓间充质干细胞来源的 EXOs 中的 miR-1246 通过抑制 NF- $\kappa$ B P65 从而促进 M2 型巨噬细胞的极化;根尖牙乳头间充质干细胞来源的 EXOs 通过促进 DNA 去甲基化酶 Tet2(Tet methylcytosine dioxygenase 2, Tet2)介导的 FoxP3 的去甲基化,维持 FoxP3 的稳定表达,促进 Treg 转化,从而缓解牙周炎局部炎症。此外炎症相关因子可以影响牙源性间充质干细胞来源的外泌体的免疫调节活性,如 LPS 预处理的牙髓间充质干细胞来源的 EXOs 可通过 ROS/JNK 信号通路降低 RANKL/OPG 比例,并通过 ROS/ERK 信号通路促进巨噬细胞向 M2 型极化;肿瘤坏死因子- $\alpha$  和干扰素- $\alpha$  两种促炎细胞因子预处理的牙龈间充质干细胞来源的 EXOs 通过高表达 CD73 和 CD5L 从而促进 M2 型巨噬细胞的极化;牙周炎患者 PDLSCs 来源的 EXOs 促进巨噬细胞向 M1 型极化。本文综述 DMSCs 来源的 EXOs 在牙周免疫调节过程中对两种细胞平衡转化影响的研究进展,为 EXOs 治疗牙周炎提供参考。

**【关键词】** 牙周炎; 牙源性间充质干细胞; 外泌体; M1型巨噬细胞; M2型巨噬细胞; Th17细胞; Treg细胞; 免疫调节

**【中图分类号】** R78 **【文献标志码】** A **【文章编号】** 2096-1456(2024)10-0798-07

**【引用著录格式】** 阿克帕尔·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): 798- . doi:10.12016/j.issn.2096-1456.2024.202330506.

## Research progress on dental mesenchymal stem cell-derived exosomes in periodontal immune regulation

Akbar·arkin<sup>1</sup>, Chen Xiaotao<sup>2</sup>. 1. College of Life Sciences, Xinjiang University, Urumqi 830000, China; 2. Department of Stomatology, People's Hospital of Xinjiang Uygur Autonomous Region, Urumqi 830000, China

Corresponding author: Chen Xiaotao, Email: 1440945785@qq.com, Tel: 86-1599112966

**【Abstract】** Exosomes (EXOs) are important mediators of intercellular communication that contain a variety of substances, including miRNA, mRNA, DNA, and protein molecules, which can act on target cells and have broad medical prospects as “cell-free therapy”. The inclusion of EXOs varies with the type and state of the donor cell, thus EXOs from different cell types may exhibit different biological effects. Dental mesenchymal stem cell (DMSC)-derived EXOs (DMSC-EXOs) have gained increasing research attention in the fields of tissue regenerative medicine and immune regulation.

**【收稿日期】** 2023-10-26; **【修回日期】** 2024-06-24

**【基金项目】** 国家自然科学基金项目(82260195)

**【作者简介】** 阿克帕尔·艾尔肯, 硕士, Email: 635981565@qq.com

**【通讯作者】** 陈晓涛, 教授, 博士, Email: 1440945785@qq.com, Tel: 86-1599112966



微信公众号

Current research on EXOs is focused on the homeostasis between proinflammatory (M1)/anti-inflammatory (M2) macrophages and T-helper 17 (Th17)/regulatory T (Treg) cells during periodontal immune regulation. Studies have shown that DMSC-EXOs can promote the transformation of macrophages and T cells and that this function may be dependent on the surrounding microenvironment and the tissue origin of stem cells. For instance, miR-1246 in dental pulp stem cell-derived EXOs promotes M2 macrophage polarization by inhibiting nuclear factor kappa-B (NF- $\kappa$ B) p65. Meanwhile, EXOs derived from stem cells from apical papilla promote DNA demethylase Tet2-mediated demethylation of FoxP3, maintain stable FoxP3 expression, and promote Treg cell transformation, thus alleviating local inflammation in periodontitis. In addition, the immunomodulatory activities of DMSC-EXOs can be affected by inflammatory factors. For example, EXOs derived from lipopolysaccharide-preconditioned dental follicle stem cells can reduce the receptor activator of NF- $\kappa$ B ligand/osteoprotegerin ratio through the reactive oxygen species (ROS)/c-Jun N-terminal kinase signaling pathway and promote M2 macrophage polarization through the ROS/extracellular signal-regulated kinase signaling pathway. Additionally, EXOs derived from gingiva-derived mesenchymal stem cells pretreated with tumor necrosis factor- $\alpha$  and interferon- $\alpha$  proinflammatory cytokines can promote M2 macrophage polarization through high expression of CD73 and CD5L, while EXOs derived from periodontal ligament stem cells can promote M1 macrophage polarization. This article reviews the research progress on the immunoregulation and effects of DMSC-EXOs on the homeostasis of M1/M2 macrophages and Th17/Treg cells during periodontal immune regulation and provides a reference for the treatment of periodontitis using DMSC-EXOs.

**【Key words】** periodontitis; dental mesenchymal stem cells; exosome; M1 macrophage; M2 type macrophage; Th17 cells; Treg cells; immunomodulation

**J Prev Treat Stomatol Dis, 2024, 32(10): 00-00.**

**【Competing interests】** The authors declare no competing interests.

This study was supported by the grants from National Natural Science Foundation of China (No. 82260195).

研究表明,牙周炎的起因为牙菌斑生物膜,而宿主免疫的过度炎症反应通常是加重牙周炎和促进牙周组织破坏的主要因素<sup>[1-2]</sup>。因此,调节宿主免疫反应被认为是治疗牙周炎并促进牙周组织再生的一种新方法<sup>[3]</sup>。间充质干细胞(mesenchymal stem cells, MSCs)是存在于骨髓、脐带、脂肪和牙周等多种组织中的多功能干细胞<sup>[4]</sup>。MSCs除了具有自我更新和促进组织再生能力外,还具有通过直接接触或旁分泌在炎症和损伤部位进行调节免疫反应的能力<sup>[5]</sup>。牙源性间充质干细胞(dental mesenchymal stem cells, DMSCs)作为间充质干细胞的一种亚型同样具有强大的免疫调节作用,在急性肺或脑损伤、急性呼吸窘迫综合征等急性炎症性及免疫相关性疾病中具有极大的治疗潜力<sup>[6]</sup>。研究表明 DMSCs 可通过细胞间的直接接触或通过分泌可溶性因子、细胞外囊泡等调控多种免疫细胞功能,从而起到免疫调节作用<sup>[7]</sup>。外泌体(exosomes, EXOs)作为最重要的细胞外囊泡之一,已受到学者高度关注,尤其是其内容物(包括细胞因子、生长因子、mRNA、miRNA 和 DNA 等)在细胞间通信中的重要作用<sup>[8]</sup>。MSCs 来源的外泌体具有与 MSCs 相似的生物学效应,并且比 MSCs 更稳定和易

于保存,并且来源于不同细胞以及不同微环境的 EXOs 具有不同的生物学功能,其携带的内容物均与它们存在的微环境紧密相关<sup>[9]</sup>。牙源性间充质干细胞来源的外泌体(DMSCs-EXOs)具有很强的促组织再生以及免疫调节功能,可为牙周炎提供一种新的治疗方法<sup>[10]</sup>。笔者对牙源性间充质干细胞来源的外泌体在牙周免疫调节过程中的研究进展作一综述,为外泌体治疗牙周炎提供参考。

## 1 牙源性间充质干细胞及其来源的外泌体

牙源性间充质干细胞分布于口腔不同的组织,包括牙周膜、脱落的乳牙、牙髓、根尖乳头和牙囊等<sup>[11]</sup>。目前为止,已分离并鉴定了牙髓间充质干细胞(dental pulp stem cells, DPSCs)、脱落乳牙间充质干细胞(stem cells from exfoliated deciduous teeth, SHED)、牙周膜间充质干细胞(periodontal ligament stem cells, PDLSCs)、牙囊间充质干细胞(dental follicle progenitor cells, DFPCs)、以及根尖乳头间充质干细胞(apical papilla stem cells, SCAPs)<sup>[12]</sup>。DMSCs 作为 MSCs 的亚型也同样具有自我更新能力和多向分化潜能,同时可介导各种免疫细胞的活性<sup>[13]</sup>。最近研究表明与来自骨髓或

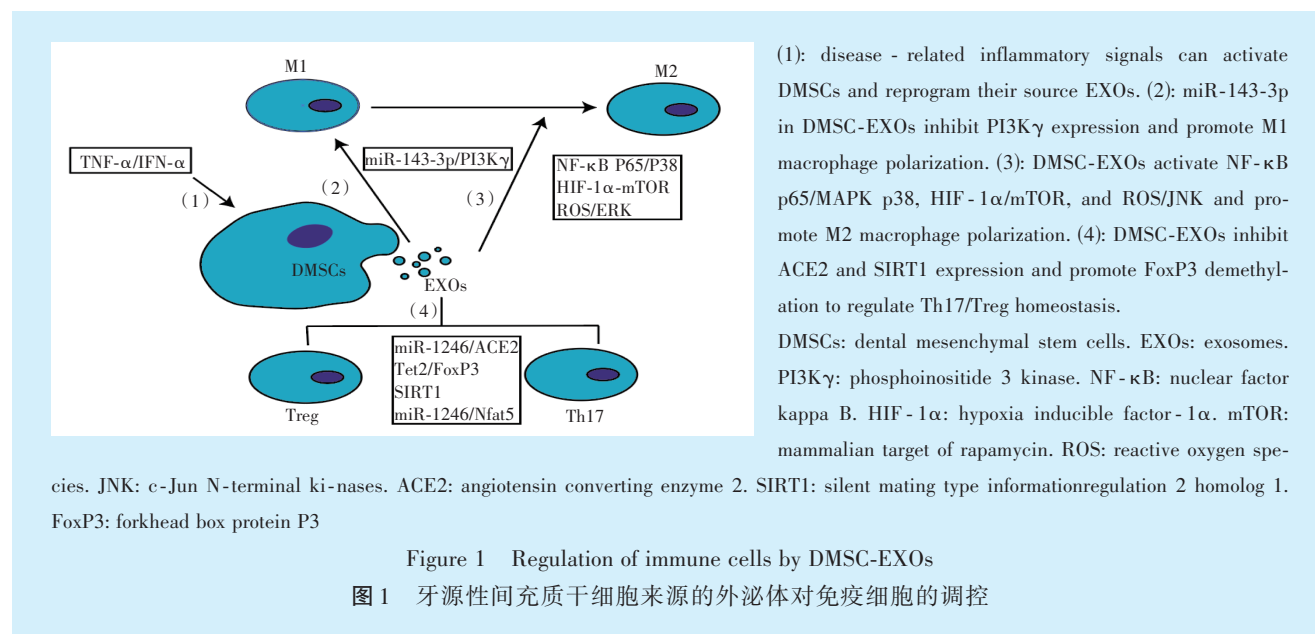
其他来源的MSCs相比,DMSCs可通过非侵入性方法获取,并表现出较强的免疫调节能力,这可能是由于口腔内频繁接触炎症环境所致<sup>[14]</sup>。此外,DMSCs均来自于颅神经嵴细胞,其独特的组织特异性使其在牙髓牙本质再生、神经再生性疾病、牙周组织再生以及其他难治性疾病方面具有潜在的优势<sup>[15]</sup>。研究表明,DMSCs可通过细胞间直接接触和分泌可溶性因子作用于免疫系统中巨噬细胞、T细胞、B细胞、自然杀伤细胞、树突状细胞等关键成分的功能活性<sup>[16]</sup>,关于这些机制已有了详细的综述<sup>[17]</sup>。目前,更多研究表明DMSCs的免疫调节功能主要归因于其来源的EXOs。EXOs是直径30~150 nm的胞外小囊泡,其内携带母细胞来源的蛋白、miRNA、核酸等遗传物质,是细胞间通讯的新机制,在免疫调节、肿瘤生长和浸润、病毒传播以及组织再生等多种病理生理过程中发挥重要作用<sup>[18]</sup>。几乎所有类型的细胞都分泌EXOs,包括MSCs、树突状细胞(dendritic cell, DCs)、B细胞、T细胞等<sup>[19]</sup>,并广泛存在于许多体液中,如血浆、尿液、母乳、精液、羊水和唾液<sup>[20]</sup>。研究发现,EXOs可通过3种途径调控靶细胞的活性:①EXOs通过靶细胞的胞吞作用将活性物质及信息释放到靶细胞内;②外泌体膜蛋白与靶细胞表面蛋白相结合,

激活细胞内信号通路,从而调控靶细胞活性;③外泌体膜蛋白可被细胞外间隙的蛋白酶切割,裂解的片段可作为可溶性配体,与目标细胞表面受体结合,完成信息传递<sup>[21]</sup>。由于EXOs的内含物可以根据疾病状态重新编程,EXOs越来越多地被用于疾病诊断和预后的潜在诊断性生物标志物<sup>[22]</sup>。

DMSCs-EXOs在各种临床前和临床研究中显示出良好的潜力,包括牙周炎的诊断和治疗<sup>[23]</sup>。DMSCs-EXOs在牙周炎中主要发挥抑制炎症反应和促进牙周组织再生的作用,为治疗牙周炎和改善牙槽丢失提供了一种新的视角和潜在的治疗方法<sup>[24]</sup>。

## 2 牙源性间充质干细胞来源的外泌体在牙周免疫调节中的作用

牙周炎免疫治疗的主要靶点是参与牙周免疫调节的免疫细胞及其产物<sup>[25]</sup>。通过调节不同水平的免疫细胞,从而抑制促炎细胞亚群的分化和促炎细胞因子的合成、促进抗炎细胞亚群的分化和抗炎细胞因子的合成<sup>[26]</sup>。目前,促炎型(M1型)/抗炎型(M2型)巨噬细胞、辅助性T细胞(Th17)/调节性T细胞(Treg)之间的平衡转化是牙周炎免疫调节的研究热点(图1)<sup>[27]</sup>。



### 2.1 DMSCs-EXOs对牙周巨噬细胞的调控

巨噬细胞的行为变化与组织微环境密切相关,组织微环境可使巨噬细胞发生表型和功能变化<sup>[28]</sup>。研究发现在牙周炎微环境中巨噬细胞倾向于向M1(proinflammatory)型(促炎型)分化,而M2

(pro-repairing)型(抗炎型)的分化被明显抑制<sup>[29]</sup>。M1型巨噬细胞可释放多种炎症细胞因子如肿瘤坏死因子- $\alpha$ (tumor necrosis factor $\alpha$ , TNF- $\alpha$ )、白介素(interleukin, IL)-6和IL-1 $\beta$ 等,引起牙龈炎症和牙槽骨吸收<sup>[30]</sup>。M2型巨噬细胞可通过分泌IL-10

和转化生长因子- $\beta 1$  (transform growth factor- $\beta 1$ , TGF- $\beta 1$ )等抗炎因子降低炎症反应,促进细胞增殖和组织再生<sup>[31]</sup>。因此,巨噬细胞的可塑性是牙周炎免疫调控的主要靶点。

牙周炎中 DMSCs-EXOs 的一个重要免疫调节特性是抑制 M1 型巨噬细胞的极化、促进 M2 型巨噬细胞极化,增强抗炎细胞因子的表达,从而降低局部的炎性反应<sup>[32]</sup>。Shen 等<sup>[33]</sup>通过提取人牙髓间充质干细胞来源的外泌体(DPSCs-EXOs)并将其与壳聚糖水凝胶结合,在体内检测负载外泌体的水凝胶(EXOs/CS)在小鼠牙周炎模型中对巨噬细胞的极化影响,结果表明 EXOs/CS 能够促进牙周炎小鼠牙周组织中巨噬细胞从 M1 型转化为 M2 型,显著降低 IL-23、IL-1 $\alpha$ 、TNF- $\alpha$ 、IL-12、IL-1 $\beta$ 、IL-27 和 IL-17 等炎症因子的表达,从而促进牙周炎小鼠的牙槽骨和牙周上皮的愈合,其机制可能与 DPSCs-EXOs 中的 miR-1246 抑制 NF- $\kappa$ B P65 和 P38 有关,该研究结果不仅揭示了 DPSCs-EXOs/CS 的治疗机制,而且为开发有效的牙周炎治疗方法提供了基础。

近年来,如何提高 DMSCs-EXOs 的免疫调节能力成为研究的热点。间接将靶细胞预处理再从培养上清液中提取功能化 EXOs 是 EXOs 疗法的应用策略之一。Huang 等<sup>[34]</sup>的研究发现 LPS 预处理牙囊间充质干细胞来源的外泌体(LPS-DFSCs-EXOs)可通过活性氧(reactive oxygen species, ROS)/c-Jun 氨基末端激酶(c-Jun N-terminal kinase, JNK)信号通路降低核因子  $\kappa$ B 受体活化因子配体(receptor activator of nuclear factor- $\kappa$ B ligand, RANKL)/骨保护素(osteoclastogenesis inhibitory factor, OPG)比例,并通过 ROS/细胞外调节蛋白激酶(extracellular regulated protein kinases, ERK)信号通路促进巨噬细胞向 M2 型极化,从而增强 DFSCs-EXOs 对牙周炎的治疗效果。这些结果表明炎症相关因子能够增强 DMSCs-EXOs 促进巨噬细胞 M2 型极化的能力。然而,Wang 等<sup>[35]</sup>的研究发现 DMSCs-EXOs 的免疫调节能力在体内与其上述研究者的结果相反。将牙周炎患者的 PDLSCs (inflammatory periodontal ligament stem cells, iPDLSCs) 和人急性单核细胞白血病细胞(THP-1)来源的 M0 巨噬细胞共培养后发现,iPDLSCs 在 mRNA 和蛋白水平上抑制了 M2 型巨噬细胞极化;进一步分离 iPDLSCs 来源的外泌体(iPDLSCs-EXOs),发现 iPDLSCs-EXOs 抑制 M2 型巨噬细胞的同时通过 iPDLSCs-EXOs 促进巨噬细胞向

M1 表型极化。利用 miRNA 芯片比较 PDLSCs-EXOs 和 iPDLSCs-EXOs 的 miRNA,发现与 PDLSCs-EXOs 相比 iPDLSCs-EXOs 中富集了 miR-143-3p,而 miR-143-3p 通过抑制 PI3K/AKT 信号通路并激活 NF- $\kappa$ B 信号通路,从而抑制 PI3K $\gamma$  的表达,促进 M1 巨噬细胞极化,加重牙周炎小鼠模型的牙周炎症。DMSCs-EXOs 在炎症微环境中对巨噬细胞的极化产生相反的结果可能是因为:①外泌体来源的细胞类型不同;②体内外炎症微环境对 EXOs 所含内含物产生不同的影响。因此,炎症微环境在体内外对 DMSCs-EXOs 免疫调节能力的影响需要进一步探讨,并阐明其临床意义和调节巨噬细胞极化的详细机制。

## 2.2 DMSCs-EXOs 对牙周 T 细胞的调控

随着对 T 细胞在牙周炎免疫调节作用中的认识逐渐深入,发现牙周炎局部免疫反应平衡的破坏与 Th17/Treg 细胞之间比例的失调密切相关<sup>[36]</sup>。据报道,牙周组织中 Th17 和 Treg 细胞的失衡以及外周血中 Th17/Treg 比值的升高与牙周炎的进展和牙槽骨吸收密切相关<sup>[37]</sup>。Dutzan 等<sup>[38]</sup>研究表明在牙周炎中 Th17 细胞及其细胞因子表达上调,并与牙周组织破坏呈正相关。Glawacki 等<sup>[39]</sup>发现在犬牙周炎模型中招募 Treg 可通过降低促炎因子(包括 TNF- $\alpha$ 、IL-1 $\beta$  和 IL-17)的释放来显著减少犬牙周炎模型的牙槽骨丢失。因此,调节 Th17/Treg 比值可能是治疗牙周炎的新途径。

牙周炎中 DMSCs-EXOs 对 T 细胞转化的影响,是其维持牙周免疫稳态的重要途径之一<sup>[40]</sup>。SCAPs-EXOs 通过促进 DNA 去甲基化酶 Tet2 (Tet methylcytosine dioxygenase 2, Tet2)介导的 FoxP3 的去甲基化,维持 FoxP3 的稳定表达,促进 Treg 转化,从而缓解牙周炎局部炎症<sup>[41]</sup>。然而,SCAP-EXO 上调 Tet2 的具体机制尚不清楚,需进一步研究探讨其机制。在体外炎症模拟环境中,与 PDLSCs-EXO 相比 LPS-PDLSCs-EXO 中 miR-155-5p 的表达显著降低,与 CD4<sup>+</sup> T 细胞共培养导致其组蛋白去乙酰化酶 1 (SIRT1) 表达增加,从而促进 CD4<sup>+</sup> T 细胞向 Treg 分化<sup>[42]</sup>。虽然 DMSCs-EXOs 已被证明在实验性牙周炎中具有治疗作用,但其产量低、疗效有限等缺点阻碍了其临床应用,因此,Yu<sup>[43]</sup>和 Zhang<sup>[44]</sup>等尝试用 3D 培养方法取代传统的 2D 培养,发现 3D 培养可促进 DPSCs 分泌 EXO,同时 3D-DPSCs-EXOs 在牙周炎模型中可以通过 miR-1246/Nfat5 轴调节 T17/Treg 的平衡,恢复受损牙周组织的免疫应

答<sup>[44]</sup>。结果表明与2D培养相比,3D培养可以提高 DPSCs-EXO<sub>s</sub>的产量,并增强其免疫调节能力。

### 3 展 望

作为传统疗法的补充,通过调节宿主免疫反应来治疗牙周炎在近几十年受到了广泛关注<sup>[45]</sup>, EXO<sub>s</sub>在某种程度上可取代 MSCs,为免疫治疗打开了新的治疗视角<sup>[46-47]</sup>。相比于直接应用 MSCs 治疗,EXO<sub>s</sub>具有以下潜在优势:①EXO<sub>s</sub>免疫原性比 MSCs 低;②EXO<sub>s</sub>治疗可以有效避免直接应用 MSCs 治疗带来的相关安全性问题,并且 EXO<sub>s</sub>易于制备和运输;③EXO<sub>s</sub>作为纳米颗粒,可以穿过多种屏障(如血脑屏障、毛细血管等),且可以直接被靶细胞摄取并作用于靶细胞,作用效率更高。但 EXO<sub>s</sub>在临床转化、大规模生产、稳定的制备、存储方案和质量控制方面仍存在必须克服的挑战。值

得注意的是,不同的分离技术会影响 EXO<sub>s</sub>的纯度、产量甚至生物活性<sup>[44]</sup>。因此,进一步开发 EXO<sub>s</sub>分离、纯化以及提高其产量的新技术将有助于克服这些缺点。研究表明,DMSCs-EXO<sub>s</sub>通过调控免疫细胞的活性,进而影响机体的先天免疫系统和适应性免疫系统<sup>[48]</sup>。虽然 DMSCs-EXO<sub>s</sub>的免疫调节能力具有广阔的应用前景已被广泛认可,目前 DMSCs-EXO<sub>s</sub>的研究仍处早期阶段,针对其在牙周免疫调节中的研究相对较少(表1),停留在细胞分子以及动物实验等基础研究阶段,除巨噬细胞和 T 细胞外,中性粒细胞<sup>[49]</sup>、B 细胞<sup>[50]</sup>、肥大细胞<sup>[51]</sup>和树突状细胞<sup>[52]</sup>都等免疫细胞均参与了牙周免疫反应,以上免疫细胞在牙周炎中的作用不可忽视,但目前还没有详细和广泛的研究探讨 DMSCs-EXO<sub>s</sub>对这些细胞的调控。

表1 牙源性间充质干细胞来源的外泌体牙周免疫调节特性

Table 1 Periodontal immune regulation properties of DMSC-EXO<sub>s</sub>

Immune cell type	Exosome source	Mechanisms	References
Macrophage	DPSC-EXO <sub>s</sub>	miR-1246 inhibits the expression of NF-κB p65, MAPK p38, and inflammatory factors, such as IL-23, IL-1α, TNF-α, IL-12, IL-1β, IL-27, and IL-17, thereby promoting the transformation of macrophages from M1 to M2 type	[33]
	DFSP-EXO <sub>s</sub>	ROS/ERK signaling pathway promotes macrophage polarization to M2 type	[34]
	iPDLSC-EXO <sub>s</sub>	miR-143-3p inhibits the expression of PI3Kγ and promotes the polarization of M1 macrophages by inhibiting the PI3K/AKT signaling pathway and activating the NF-κB signaling pathway	[35]
T cell	SCAP-EXO <sub>s</sub>	Promote DNA demethylase Tet2-mediated demethylation of FoxP3, maintain stable FoxP3 expression, and promote Treg cells transformation	[41]
	PDLSC-EXO <sub>s</sub>	Inhibit SIRT1 expression and promote Treg cell transformation of CD4 <sup>+</sup> T cells	[42]
	3D-DPSC-EXO <sub>s</sub>	miR-1246/NFAT5 axis regulates T17/Treg cell homeostasis	[43][44]

DMSC-EXO<sub>s</sub>: exosomes derived from dental mesenchymal stem cells. NF-κB: nuclear factor kappa B; IL: interleukin; HIF-1α: hypoxia inducible factor-1α; mTOR: mammalian target of rapamycin; TNF-α: tumor necrosis factor alpha; ROS: reactive oxygen species; ERK: extracellular regulated protein kinases; PI3K: phosphoinositide 3 kinase; Tet2: Tet methylcytosine dioxygenase 2; FoxP3: forkhead box protein P3; Treg: regulatory T cells

**【Author contributions】** Akbar·arkin collected the references and wrote the article. Chen XT conceptualized, revised and reviewed the article. All authors read and approved the final manuscript submitted.

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