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·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

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【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-κB 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EXOs的免疫调节活性，如脂多糖预处理的牙囊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-α和干扰素-α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；牙周炎患者牙周膜间充质干细胞来源的EXOs促进巨噬细胞向M1表型极化。本文综述牙源性间充质干细胞来源的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
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Research progress on dental mesenchymal stem cell-derived exosomes in periodontal immune regulation

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【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.

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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-κB) 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-κB 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-α and interferon-α proinflammatory cytokines can promote M2 macrophage polarization through high expression of CD73 and CD5L, while EXOs derived from inflammatory 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 macrophage; Th17 cells; Treg cells; immunomodulation

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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[1-2]。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[3]。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[4]。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[5]。牙源性间充质干细胞（dental mesenchymal stem cells，DMSCs）作为MSCs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的治疗具有极大潜力[6]。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[7]。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[8]。MSCs来源的EXOs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[9]。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[10]。笔者对DMSCs-EXOs在牙周免疫调节过程中的研究进展进行综述，为EXOs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

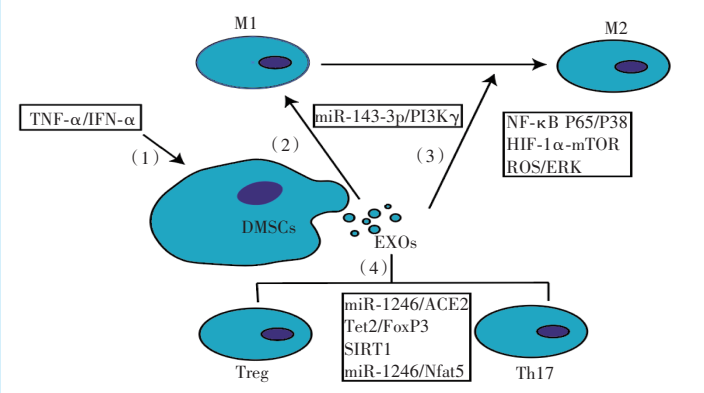
DMSCs分布于口腔不同的组织，包括牙周膜、脱落的乳牙、牙髓、根尖乳头和牙囊等[11]。目前为止，已分离并鉴定了牙髓间充质干细胞（dental pulp stem cells，DPSCs）、脱落乳牙间充质干细胞（stem cells from exfoliated deciduous teeth，SHED）、牙周膜间充质干细胞（periodontal ligament stem cells，PDLSCs）、牙囊间充质干细胞（dental follicle stem cells，DFSCs）、以及根尖牙乳头间充质干细胞（apical papilla stem cells，SCAPs）[12]。DMSCs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[13]。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[14]。此外，DMSCs均来自头颅神经嵴细胞，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[15]。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[16]，关于这些机制已有了详细的综述[17]。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[18]。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[19]，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[20]。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；②EXOs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；③EXOs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[21]。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[22]。

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[23]。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骨吸收提供了一种新的视角和潜在的治疗方法[24]。

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控的免疫细胞及其产物[25]。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[26]。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）[27]。



(1): disease - related inflammatory signals can activate DMSCs and reprogram their source EXOs. (2): miR-143-3p in DMSC-EXOs inhibit PI3Kγ expression and promote M1 macrophage polarization. (3): DMSC-EXOs activate NF-κB p65/MAPK p38, HIF-1α/mTOR, and ROS/JNK and promote M2 macrophage polarization. (4): DMSC-EXOs inhibit ACE2 and SIRT1 expression and promote FoxP3 demethylation to regulate Th17/Treg homeostasis.

DMSCs: dental mesenchymal stem cells. EXOs: exosomes. PI3Kγ: phosphoinositide 3 kinase. NF-κB: nuclear factor kappa B. HIF-1α: hypoxia inducible factor-1α. mTOR: mammalian target of rapamycin. ROS: reactive oxygen species. JNK: c-Jun N-terminal ki-nases. ACE2: angiotensin converting enzyme 2. SIRT1: silent mating type information regulation 2 homolog 1. FoxP3: forkhead box protein P3

Figure 1　Regulation of immune cells by DMSC-EXOs

图1　牙源性间充质干细胞来源的外泌体对免疫细胞的调控

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[28]。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[29]。M1型巨噬细胞可释放多种炎性细胞因子如肿瘤坏死因子-α（tumor necrosis factoralpha，TNF-α）、白介素（interleukin，IL）-6和IL-1β等，引起牙龈炎症和牙槽骨吸收[30]。M2型巨噬细胞可通过分泌IL-10

和转化生长因子-β1(transform growth factor-β1，TGF-β1)等抗炎因子降低炎症反应，促进细胞增殖和组织再生[31]。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[32]。Shen等[33]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EXOs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-1α、TNF-α、IL-12、IL-1β、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-κB P65和P38有关，该研究结果不仅揭示了DPSCs-EXOs/CS的治疗机制，而且为探索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[34]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κB受体活化因子配体(receptor activator of nuclear factor-κB 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[35]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型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-κB信号通路，从而抑制PI3Kγ的表达，促进M1型巨噬细胞极化，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：①EXOs来源的细胞类型不同；②体内外炎症微环境对EXOs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　牙源性间充质干细胞来源的外泌体对牙周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和Treg细胞之间比例的失调密切相关[36]。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[37]。Dutzan等[38]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。Glowacki等[39]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-α、IL-1β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[40]。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[41]。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$CD4^+$ 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$CD4^+$ T细胞向Treg分化[42]。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等[43]和Zhang等[44]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Th17/Treg的平衡，恢复受损牙周组织的免疫应答[44]。结果表明与2D培养相比，3D培养可以提高DPSCs-EXOs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[45]，EXOs在某种程度上可取代MSCs，为免疫治疗打开了新的治疗视角[46-47]。相比于直接应用MSCs治疗，EXOs具有以下潜在优势：①EXOs免疫原性比MSCs低；②EXOs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EXOs易于制备和运输；③EXOs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EXOs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EXOs的纯度、产量甚至生物活性[44]。因此，进一步开发EXOs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-EXOs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[48]。虽然DMSCs-EXOs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-EXOs的研究仍处于早期阶段，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[49]、B细胞[50]、肥大细胞[51]和树突状细胞[52]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-EXOs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-EXOs

Immune cell type	Exosome source	Mechanisms	References
Macrophage	DPSC-EXOs	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]
	DFSC-EXOs	ROS/ERK signaling pathway promotes macrophage polarization to M2 type	[34]
	iPDLSC-EXOs	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-EXOs	Promote DNA demethylase Tet2-mediated demethylation of FoxP3, maintain stable FoxP3 expression, and promote Treg cells transformation	[41]
	PDLSC-EXOs	Inhibit SIRT1 expression and promote Treg cell transformation of $CD4^+$ T cells	[42]
	3D-DPSC-EXOs	miR-1246/NFAT5 axis regulates T17/Treg cell homeostasis	[43][44]

DMSC-EXOs: exosomes derived from dental mesenchymal stem cells. DPSC: dental pulp stem cell. DFSC: dental follicle stem cell. iPDLSC: inflammatory periodontal ligament stem cell. SCAP: apical papilla stem cell. PDLSC: periodontal ligament stem cell. 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

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