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· 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

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【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 $\text{INF-}\gamma$ 、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。骨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

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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 Medicine Plus & Department of Periodontics, West China Hospital of Stomatology, Sichuan University, Chengdu 610041, China
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【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 $\text{INF-}\gamma$ 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

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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

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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- γ T,它与信号转导与转录激活子(signal transducer and activator of transcription, 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-1 β 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-1 β 、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 of nuclear 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- γ T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

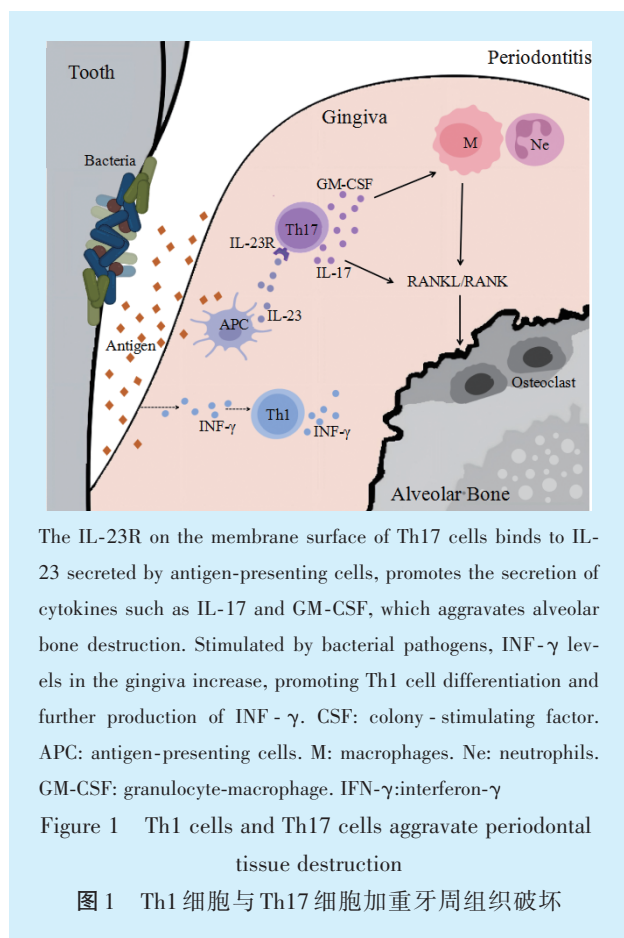
生发展的机制,而Th17-Treg平衡极大地补充了Th细胞在牙周炎中的作用。近来的研究表明,牙周炎中Th1细胞、Th17细胞水平升高,Th2细胞、Tregs水平降低^[21]。

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,



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, ROR γ t) 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

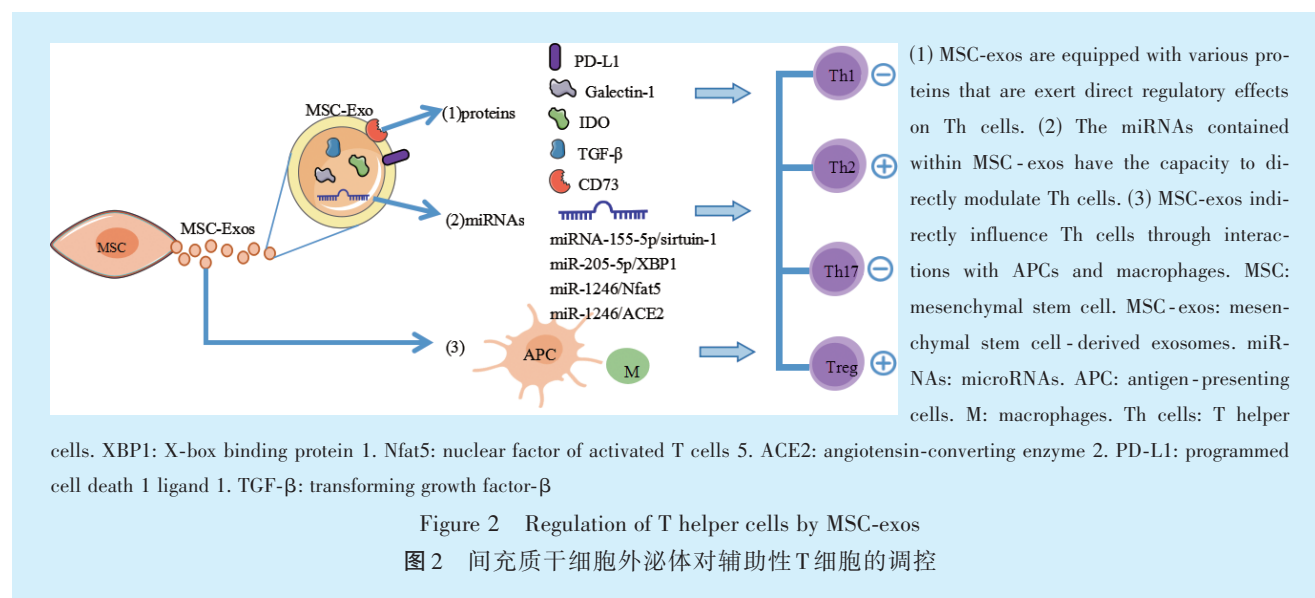
通过维持 FOXP3 和 SMAD 的表达促使幼稚的 CD4 阳性 T 淋巴细胞或 Th17 细胞向 Tregs 分化^[51]。IDO 是一种双加氧酶,研究发现具有较高 IDO 含量的 MSC-exos 可以抑制 Th17 细胞、促进 Tregs 分化,调控 Th17-Treg 细胞平衡^[52]。MSC-exos 膜表面的 CD73 具有单磷酸腺苷(AMP)酶活性,催化活化 T 细胞中的大量 AMP 分解产生腺苷,Th1 细胞内存在腺苷 2A 受体,与腺苷结合促进自身凋亡,从而降低 TNF- α 和 IFN- γ 水平^[45]。

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 培养骨髓干细胞,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。



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、移植后再生产效率降低、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。

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