

[文章编号] 1671-587X(2026)02-0543-08

DOI:10.13481/j.1671-587X.20260228

外泌体在口腔疾病诊断及治疗中应用的研究进展

李 恬, 王家凤, 张志民

(吉林大学口腔医院牙体牙髓科, 吉林 长春 130021)

[摘 要] 外泌体是一类包含脂质、核酸和蛋白质的膜性囊泡, 可转运多种生物活性分子, 在生理和病理进程中发挥关键调节效能。随着对外泌体作用机制的深入研究, 外泌体已被证实在口腔疾病中具备潜在的诊断和治疗价值。基于从唾液、血清和血浆等体液中提取外泌体的液体活检技术显示, 外泌体在口腔疾病的早期诊断及病程监测方面展现出广阔的发展潜能。在口腔鳞状细胞癌、牙周炎、口腔扁平苔藓和原发性干燥综合征等疾病中, 外泌体所携带的微小 RNA (miRNA) 及蛋白质等成分呈现出特征性的表达差异, 因此具备成为诊断生物标志物的潜力。此外, 外泌体在促进组织再生、调节免疫及递送药物等方面表现出的多元功能, 也为牙髓炎、牙周炎及组织损伤等口腔疾病的治疗开辟了新路径。本文深入探讨外泌体在口腔疾病诊断和治疗中的应用进展, 以期对口腔疾病的预防、诊断及治疗提供理论基础。

[关键词] 外泌体; 口腔疾病; 液体活检; 生物标志物; 组织再生; 免疫调节; 药物递送

[中图分类号] R78 **[文献标志码]** A

Research progress in application of exosomes in diagnosis and treatment of oral diseases

LI Tian, WANG Jiafeng, ZHANG Zhimin

(Department of Dentistry and Endodontics, Stomatology Hospital, Jilin University,
Changchun 130021, China)

ABSTRACT Exosomes are a class of membranous vesicles containing lipids, nucleic acids, and proteins, which are capable of transporting various bioactive molecules and play key regulatory roles in physiological and pathological processes. With in-depth research into the mechanisms of action, exosomes have been demonstrated to possess the potential diagnostic and therapeutic value in oral diseases. Liquid biopsy techniques based on the extraction of exosomes from body fluids such as saliva, serum, and plasma have revealed the broad potential for exosomes in the early diagnosis and disease progression monitoring of oral conditions. In diseases such as oral squamous cell carcinoma, periodontitis, oral lichen planus, and primary Sjögren's syndrome, components carried by exosomes, including microRNA (miRNA) and proteins, exhibit characteristic differences in their expressions, thereby holding potential as diagnostic biomarkers. Furthermore, the diverse functions of exosomes in promoting tissue regeneration, modulating immunity,

[收稿日期] 2024-10-21 **[录用日期]** 2024-12-19

[基金项目] 国家自然科学基金项目 (22204056)

[作者简介] 李 恬 (2000—), 女, 湖南省常德市人, 在读硕士研究生, 主要从事牙体牙髓疾病基础和临床方面的研究。

[通信作者] 王家凤, 副教授 (E-mail: wangjiafeng@jlu.edu.cn);

张志民, 教授, 博士研究生导师 (E-mail: zhangzhim@jlu.edu.cn)

©《吉林大学学报(医学版)》编辑部, 开放获取遵循 CC BY-NC-ND 协议。

© Editorial Board of Journal of Jilin University (Medicine Edition). Open access under CC BY-NC-ND license.

and delivering drugs have opened new avenues for the treatment of oral diseases such as pulpitis, periodontitis, and tissue injuries. This article provided an in-depth discussion of the advances in the application of exosomes in the diagnosis and treatment of oral diseases, aiming to offer a theoretical foundation for the prevention, diagnosis, and management of these conditions.

KEYWORDS Exosome; Oral disease; Liquid biopsy; Biomarker; Tissue regeneration; Immune regulation; Drug delivery

外泌体是由细胞分泌的一类细胞外囊泡亚群,其直径为30~150 nm,具有相对稳定的脂质双分子层结构,广泛存在于唾液、血清和尿液等多种体液中。这类微小囊泡可通过循环系统分布至全身,因其体积小且可穿越血脑屏障,成为药物递送的理想载体^[1]。外泌体携带多种生物活性成分,如脂质、蛋白质、信使RNA (message RNA, mRNA)、微小RNA (microRNA, miRNA) 和环状RNA (circular RNA, circRNA) 等,其组成取决于亲本细胞的类型及状态。外泌体主要通过内吞作用、直接膜融合及受体-配体相互作用3种机制与靶细胞作用,从而在细胞间信息传递中起关键调控作用^[2]。鉴于外泌体的异质性及其传递生物活性分子的特点,其在生物医学领域的应用潜力引起了研究者广泛关注。研究^[3]表明:外泌体与炎症和肿瘤等多种疾病的发生发展有关联,可发挥早期诊断、实时监测及修复心脏和肺等组织损伤的作用。目前,外泌体相关综述多集中于探讨其在机体其他系统疾病中的作用,但针对口腔疾病的系统报道较少。因此,本文旨在综述外泌体在口腔疾病中的应用研究,总结外泌体在口腔疾病诊断和治疗中的最新进展,以期对口腔疾病的预防、诊断及治疗中的外泌体应用提供新视角。

1 外泌体在口腔疾病诊断中的应用

口腔鳞状细胞癌 (oral squamous cell cancer, OSCC)、牙周炎、口腔扁平苔藓 (oral lichen planus, OLP) 和原发性干燥综合征 (primary Sjögren syndrome, pSS) 等口腔疾病可损害患者的言语、咀嚼功能及全身健康,延迟诊断和非靶向治疗会明显影响其预后及生活质量。因此,实现这些疾病的早期诊断和精准治疗至关重要。

近年来,液体活检因其微创、无痛和高重复性等优点,已成为一种新兴的诊断方法。该技术主要通过分析从唾液、血清和血浆等体液中分离出的成分,如核酸、蛋白质及细胞外囊泡等,实现疾病评估。外泌体的数量和组成受其亲本细胞的类型、状

态及其微环境的影响。在病理状态下,亲本细胞可能发生应激、凋亡或其他不稳定状态,这些变化均可反映在外泌体中。此外,与其他生物标志物比较,外泌体特有的膜结构可保护其内容物,从而提高检测的准确性和实用性。在口腔医学领域,基于外泌体的液体活检已被证实对于多种口腔疾病的诊断和监控具有重要意义。

1.1 外泌体与 OSCC

OSCC是口腔颌面部最具侵袭性的恶性肿瘤,发病率高且生存率低。目前OSCC的诊断主要依赖于有创且耗时的组织病理活检^[4]。相比之下,基于外泌体的液体活检技术为实时监控肿瘤的发生发展提供了新策略^[5]。目前,OSCC诊断相关研究主要集中于来自OSCC患者的唾液、血浆或血清中的外泌体,尤其是这些外泌体在转录组和蛋白质组层面的特征。外泌体miRNA的异常表达可反映肿瘤细胞的生物学特征,具有诊断和预测OSCC预后的潜力。研究^[6]显示:与健康个体比较,*miR-302b-3p*和*miR-517b-3p*仅在OSCC患者唾液外泌体中有特异性表达,而*miR-27a-3p*和*miR-512-3p*表达水平均明显升高。HE等^[7]研究显示:OSCC患者唾液外泌体中可检测到*miR-24-3p*表达水平升高,其可促进恶性细胞增殖。HOFMANN等^[8]研究表明:在血清或血浆外泌体中,OSCC患者*miR-130a*和*miR-21*表达水平升高,*miR-26*表达水平降低,这些外泌体miRNA表达水平与无疾病生存率和疾病分期有关联。

除miRNA外,OSCC患者唾液外泌体的蛋白质谱与健康对照组之间也存在明显差异,可反映疾病状态。FONTANA等^[9]对不同阶段OSCC患者的唾液外泌体进行蛋白质定量分析,鉴定出365种差异表达蛋白,其具有OSCC新型生物标志物的潜力。研究^[10]表明:与健康对照组比较,OSCC患者血清和唾液外泌体中Alix水平明显升高,血清外泌体中Alix有助于预测治疗效果和预后。因此,唾液和血液等生物体液中外泌体携带的miRNA及蛋白质等成分有可能作为筛查和监测OSCC的新型诊

断生物标志物。

1.2 外泌体与牙周炎

牙周炎是一种由牙菌斑引发的慢性炎症性疾病, 其全球发病率高, 主要特征是牙周支持组织的不可逆性破坏, 具体表现为临床附着丧失、牙周袋形成和牙槽骨吸收, 最终导致牙齿松动甚至脱落。传统诊断标准主要依赖于临床及影像学检查, 难以准确预测疾病进展和预后。因此, 寻找更加灵敏的牙周炎生物标志物对于筛查、诊断和预测牙周病进展至关重要。

研究^[11]发现: 牙周炎患者唾液和龈沟液中外泌体的含量及组成与牙周炎的发生发展有密切关联。研究^[12-13]显示: 与健康对照组比较, 牙周炎患者唾液外泌体中CD9和CD81水平明显降低, 二者与疾病状态呈负相关关系; *PD-L1* mRNA表达水平明显升高, 提示PD-L1高表达可能与牙周炎晚期有关联; *miR-140-5p*、*miR-146a-5p*和*miR-628-5p*等miRNA表达明显上调。此外, 研究^[14]表明: 与健康组和轻度牙周炎组比较, 重度牙周炎组唾液外泌体中*miR-381-3p*表达水平升高, 表明其可能反映疾病状况和严重程度。

1.3 外泌体与OLP

OLP是一种常见的口腔黏膜慢性炎症性疾病, 其临床表现复杂, 且部分患者存在癌变风险, 严重危害患者身心健康。积极预防、准确诊断和规范治疗对有效防治OLP有重要意义。外泌体miRNA的异常表达可能通过靶向参与无翅型MMTV整合位点家族蛋白(wingless-type MMTV integration site family, Wnt)/ β -连环蛋白(β -catenin)、磷脂酰肌醇3-激酶/蛋白激酶B(phosphatidylinositol-3 kinase/protein kinase B, PI3K/AKT)和核因子 κ B(nuclear factor-kappa B, NF- κ B)等炎症通路, 参与OLP的发生。BYUN等^[15]研究发现: 与健康受试者比较, OLP患者唾液外泌体中*miR-4484*表达水平明显升高, 提示其可作为OLP的潜在标志物。PENG等^[16]研究显示: 与健康受试者比较, OLP患者血浆外泌体中*miR-34a-5p*表达明显上调, 且其水平与OLP的严重程度呈正相关关系; OLP(尤其是糜烂型OLP)患者血浆外泌体miRNA可增强T细胞增殖和减轻细胞凋亡, 可能通过调节T细胞介导的炎症反应来加速OLP的发展。唾液或血浆外泌体miRNA在患者和健康个体之间的差异表达使其成为有潜力的生物标志物, 有望替代传统活检

对OLP进行早期诊断。

1.4 外泌体与pSS

pSS是一种以外分泌腺进行性破坏为特征的自身免疫性疾病, 主要表现为口干和眼干。研究^[17]发现: 活化T细胞来源的外泌体*miR-142-3p*可通过抑制钙离子通道功能和淀粉酶分泌, 损害唾液腺上皮细胞的分泌功能, 参与pSS的发生发展。pSS早期临床症状不典型, 导致诊断困难, 平均确诊时间可达4~5年^[18]。因此, 研究人员致力于从pSS患者体液中分离外泌体, 寻找可用于早期诊断pSS的生物标志物。LI等^[19]发现: pSS患者血清外泌体中*circ-IQGAP2*和*circ-ZC3H6*水平升高, 且其水平与患者临床特征、血清IgG水平和小涎腺病灶评分均有关联。研究^[18]显示: pSS模型小鼠血清外泌体中*miR-127-3p*、*miR-409-3p*和*miR-540-5p*水平上调。

2 外泌体在口腔疾病治疗中的应用

随着对外泌体在细胞间通讯、信号传递和免疫稳态中功能的深入理解, 外泌体在口腔疾病治疗领域的研究应用也日益增多。外泌体不仅具有促进组织再生的潜能, 还可参与免疫调节过程, 并可作为药物递送载体。

2.1 促进组织再生

间充质干细胞(mesenchymal stem cells, MSCs)来源的外泌体具有与亲本细胞相似的生物学功能, 可增强受损组织的修复再生能力, 同时相对于MSCs具有低免疫原性和易于获得及存储等优点, 在组织再生领域显示出巨大应用前景^[20]。

2.1.1 牙髓-牙本质复合体再生 创伤和感染等多种原因均可导致牙髓-牙本质复合体病变, 有效的牙髓-牙本质复合体再生能够提高牙齿对外界刺激的抵抗能力, 有助于保持牙齿的功能和健康。MSCs来源的外泌体, 尤其是牙髓干细胞来源的外泌体, 可通过激活p38丝裂原活化蛋白激酶(mitogen-activated protein kinase, MAPK)、转化生长因子 β (transforming growth factor- β , TGF- β)和Wnt/ β -catenin等多种信号通路, 诱导内源性干细胞向牙源性分化, 上调牙本质涎磷蛋白和碱性磷酸酶等牙源性标志物的表达^[21-23]。外泌体还可通过增强神经发生和促进血管生成等途径, 支持新生组织的生成和功能恢复^[24-25]。

2.1.2 牙周组织再生 牙周炎可破坏牙周支持组织, 导致牙齿松动甚至脱落。目前常规牙周治疗虽

可有效控制牙周炎症,但已丧失的牙周支持组织难以恢复,牙周组织再生已成为临床治疗的迫切需求。以外泌体为基础的牙周组织再生则可克服传统疗法的不足,临床应用潜力广阔。MSCs来源的外泌体可稳定骨移植微环境,促进成骨分化,加速骨重塑。此外,外泌体可能参与骨保护素(osteoprotegerin, OPG)/NF- κ B受体活化因子(receptor activator of NF- κ B, RANK)/RANK配体(RANK ligand, RANKL)信号通路,抑制破骨细胞活性,从而减缓骨吸收并促进牙周支持组织再生^[26-27]。CHEW等^[28]研究发现:MSCs来源的外泌体可通过AKT或胞外调节蛋白激酶(extracellular regulated protein kinases, ERK)信号通路激活腺苷受体,促进牙周膜干细胞迁移和增殖。研究^[29]显示:外泌体可通过激活一磷酸腺苷活化蛋白激酶(adenosine monophosphate-activated protein kinase, AMPK)信号通路来发挥作用,诱导新生血管和牙槽骨再生,进一步促进牙周组织再生,该过程有助于恢复牙周支持组织的血供和结构完整性。

2.1.3 颅颌面部骨组织再生 肿瘤、外伤或先天性疾病等原因导致的颅颌面部骨缺损通常需通过植骨进行修复。传统修复方法如自体或异体骨移植和牵张成骨等,存在骨量受限和免疫排斥等缺陷。组织工程和再生医学的发展为颅颌面部骨缺损的修复及再生提供了新思路。近年来,外泌体介导的骨组织再生已成为骨缺损修复的一种替代策略。

研究^[30-31]显示:外泌体可能通过携带的miRNA激活骨形成蛋白和PI3K/AKT等信号通路,募集内源性间充质干细胞到骨缺损部位,促进其增殖及分化,进而促进骨再生。此外,MSCs来源的外泌体可稳定骨移植微环境,调节炎症因子表达,调控巨噬细胞M1/M2平衡,从而参与骨缺损修复中的免疫调节,还可能通过调节OPG/RANK/RANKL信号通路来抑制破骨细胞活性,从而抑制骨吸收,加速骨缺损修复^[32-33]。

2.1.4 其他组织再生 颞下颌关节骨关节炎是一种高发的慢性退行性疾病,以进行性软骨退化、髁突重塑和滑膜炎为主要特征,以关节疼痛和功能障碍为主要症状^[34]。MSCs来源的外泌体能够减轻炎症反应,促进关节软骨细胞基质基因表达,改善髁突及软骨下结构,促进关节软骨的修复和再生。这一修复过程可能与AKT和AMPK信号通路的腺苷

活化有关联^[35-36]。

唾液腺功能障碍是一种临床多发的慢性炎症性疾病,其发生与头颈肿瘤放射治疗和pSS介导的自身免疫失调机制密切相关,患者表现出口干和吞咽障碍等症状。研究^[37]发现:骨髓干细胞衍生的外泌体通过激活G蛋白偶联雌激素受体介导的环磷腺苷/蛋白激酶A/环磷腺苷效应元件结合蛋白通路恢复pSS中的唾液腺上皮细胞功能。XIAO等^[38]研究显示:将尿源性干细胞在低氧刺激下衍生的外泌体通过尾静脉注射至放射损伤小鼠模型后,外泌体可通过Wnt3a/糖原合成激酶3 β 信号通路恢复放射损伤导致的唾液腺功能。

2.2 免疫调节

MSCs通过作用于先天性和适应性免疫系统发挥免疫调节功能。外泌体作为MSCs的重要旁分泌因子之一,在多种免疫疾病和炎症性疾病中起关键作用^[39]。MSCs来源的外泌体可通过递送miRNA和蛋白质等生物活性分子,调节炎症因子表达及免疫细胞功能,展现出良好的免疫调节潜力,在口腔炎症性疾病(如骨髓炎和牙周炎)及自身免疫性疾病的治疗中具有重要意义。

外泌体在肿瘤免疫调节中展现出复杂的双重作用^[40]。一方面,在肿瘤微环境中,外泌体可在肿瘤细胞、免疫细胞和基质细胞之间转移生物活性分子,协助肿瘤细胞逃逸免疫监视,从而促进肿瘤生长、侵袭和转移^[41]。同时,肿瘤细胞来源的外泌体可调节免疫细胞状态,导致免疫逃逸。研究^[42]显示:OSCC细胞来源的外泌体miR-29a-3p和趋化素样因子超家族成员6(chemokine-like factor-like MARVEL transmembrane domain containing member 6, CMTM6)通过激活相关信号通路诱导M2型巨噬细胞极化,进而加速肿瘤进展,提示miR-29a-3p和CMTM6可能成为OSCC免疫调节的潜在治疗靶点。另一方面,免疫细胞和MSCs来源的外泌体显示出抑制肿瘤生长、增殖及转移的潜力。树突状细胞、巨噬细胞和自然杀伤细胞等免疫细胞衍生的外泌体可激活免疫应答,抑制肿瘤发展^[43];MSCs来源的外泌体则可通过直接抑制肿瘤细胞增殖、侵袭和血管生成,进而抑制肿瘤生长^[44-45]。外泌体在肿瘤免疫调节中的多重调控作用提示其可作为重要的调节因子和潜在的治疗策略。

2.3 药物递送

外泌体凭借其良好的生物相容性与组织靶向

性, 可作为一种新兴的药物递送系统, 将药物靶向传递至目标细胞^[46]。近年来, 外泌体已作为药物递送系统应用于神经系统^[47]、心血管系统^[48]和肿瘤^[49]等多种疾病的治疗研究, 在口腔疾病靶向治疗中也展现出潜力。CUI等^[50]研究显示: 将负载褪黑素的M2型巨噬细胞来源外泌体应用于牙周炎模型大鼠, 其牙周组织的炎症程度明显减轻, 且牙槽骨缺损的修复和再生进程明显加快。DENG等^[51]研究显示: 通过共孵育将胆固醇修饰的 *miR-34a* 加载到 HEK293T 细胞的外泌体中, 该外泌体可被 OSCC 细胞摄取, 并有效抑制 OSCC 细胞增殖、迁移和侵袭。

目前, 外泌体载药方法主要分为直接修饰和间接修饰。直接修饰是指从供体细胞分离外泌体后, 通过共孵育、电穿孔、机械挤压或超声等物理化学手段将药物加载至外泌体中。这类方法各有优劣, 例如共孵育法操作简单但效率低, 电穿孔、机械挤压和超声法则可能损伤外泌体膜^[52-53]。间接修饰则是指在外泌体分泌前, 通过转染或共孵育等方法将药物导入供体细胞, 使细胞分泌含有相应药物的外泌体。其中, 转染法应用广泛, 但耗时长且转染药物具有一定的细胞毒性^[54]。除上述方法外, 近年来通过表面修饰制备工程化外泌体的研究日益增多, 旨在优化其生物活性、稳定性及靶向能力, 推动疾病个性化和精准治疗的发展^[55]。

3 总结与展望

近年来, 外泌体在口腔医学领域的研究取得显著进展。外泌体携带的生物活性分子可反映细胞状态, 在口腔疾病诊断和预后评估方面有重要价值。同时, 深入探讨外泌体在口腔疾病进展中的作用及其机制, 可为靶向治疗和组织再生修复提供坚实理论基础。尽管关于外泌体口腔疾病的研究成果较多, 但其临床转化仍面临多重挑战: ①分离与纯化的标准化。目前外泌体分离的“金标准”是超速离心法, 但其耗时耗力且产量有限^[56]。不同细胞类型和培养条件都可能影响外泌体的丰度及特性^[57]。因此, 建立统一的分离和表征标准是未来研究的关键方向。②半衰期和稳定性问题。外泌体在体内半衰期较短, 且易受到环境影响而降解, 限制其治疗效果^[58]。虽然已有研究尝试利用水凝胶^[59]和 β -磷酸三钙^[60]等生物活性支架提高外泌体的稳定性, 但如何控制外泌体的释放效率并保持其活性仍是亟待解决的技术难题。③靶向药物释放控制问题。外

泌体作为靶向药物递送系统, 其现有的载药方法在药物释放速度和定位上存在不确定性, 亟需开发新技术和材料以实现外泌体对药物的高效负载及靶向释放。

综上所述, 目前外泌体在口腔医学领域的研究已取得了重大成就, 但仍需进一步阐明其在口腔疾病发生进展中的作用机制, 并关注临床转化的可行性, 开发新的外泌体分离、纯化、分析和递送技术, 以推动外泌体在口腔临床中的应用。

利益冲突声明:

所有作者声明不存在利益冲突。

作者贡献声明:

李恬参与文献检索、论文撰写和修改, 王家凤和张志民参与选题设计、论文审阅及修改。

[参考文献]

- [1] KALLURI R, LEBLEU V S. The biology, function, and biomedical applications of exosomes [J]. *Science*, 2020, 367(6478): eaau6977.
- [2] LI Y C, ZHU Z Y, LI S C, et al. Exosomes: Compositions, biogenesis, and mechanisms in diabetic wound healing [J]. *J Nanobiotechnol*, 2024, 22(1): 398.
- [3] ABDULMALEK O A A Y, HUSAIN K H, ALI ABDULLA ALKHALIFA H K, et al. Therapeutic applications of stem cell-derived exosomes [J]. *Int J Mol Sci*, 2024, 25(6): 3562.
- [4] COSTA DOMINGUES C S D A, SERAMBEQUE B P, LARANJO CÂNDIDO M S, et al. Epithelial-mesenchymal transition and microRNAs: Challenges and future perspectives in oral cancer [J]. *Head Neck*, 2018, 40(10): 2304-2313.
- [5] MALI S B, DAHIVELKAR S. Liquid biopsy = Individualized cancer management: Diagnosis, monitoring treatment and checking recurrence and metastasis [J]. *Oral Oncol*, 2021, 123: 105588.
- [6] GAI C, CAMUSSI F, BROCCOLETTI R, et al. Salivary extracellular vesicle-associated miRNAs as potential biomarkers in oral squamous cell carcinoma [J]. *BMC Cancer*, 2018, 18(1): 439.
- [7] HE L H, PING F, FAN Z N, et al. Salivary exosomal miR-24-3p serves as a potential detective biomarker for oral squamous cell carcinoma screening [J]. *Biomed Pharmacother*, 2020, 121: 109553.
- [8] HOFMANN L, ABOU KORS T, EZIĆ J, et al. Comparison of plasma- and saliva-derived exosomal miRNA profiles reveals diagnostic potential in head and

- neck cancer[J]. *Front Cell Dev Biol*, 2022, 10: 971596.
- [9] FONTANA S, MAUCERI R, NOVARA M E, et al. Protein cargo of salivary small extracellular vesicles as potential functional signature of oral squamous cell carcinoma[J]. *Int J Mol Sci*, 2021, 22(20): 11160.
- [10] NAKAMICHI E, SAKAKURA H, MII S, et al. Detection of serum/salivary exosomal Alix in patients with oral squamous cell carcinoma[J]. *Oral Dis*, 2021, 27(3): 439-447.
- [11] SONG M Y, BAI H, ZHANG P, et al. Promising applications of human-derived saliva biomarker testing in clinical diagnostics[J]. *Int J Oral Sci*, 2023, 15(1): 2.
- [12] TOBÓN-ARROYAVE S I, CELIS-MEJÍA N, CÓRDOBA-HIDALGO M P, et al. Decreased salivary concentration of CD9 and CD81 exosome-related tetraspanins may be associated with the periodontal clinical status[J]. *J Clin Periodontol*, 2019, 46(4): 470-480.
- [13] HAN P P, BARTOLD P M, SALOMON C, et al. Salivary small extracellular vesicles associated miRNAs in periodontal status: a pilot study[J]. *Int J Mol Sci*, 2020, 21(8): 2809.
- [14] FUJIMORI K, YONEDA T, TOMOFUJI T, et al. Detection of salivary miRNAs reflecting chronic periodontitis: A pilot study[J]. *Molecules*, 2019, 24(6): 1034.
- [15] BYUN J S, HONG S H, CHOI J K, et al. Diagnostic profiling of salivary exosomal microRNAs in oral lichen planus patients[J]. *Oral Dis*, 2015, 21(8): 987-993.
- [16] PENG Q, ZHANG J, ZHOU G. Differentially circulating exosomal microRNAs expression profiling in oral lichen planus[J]. *Am J Transl Res*, 2018, 10(9): 2848-2858.
- [17] CORTES-TRONCOSO J, JANG S I, PEREZ P, et al. T cell exosome-derived miR-142-3p impairs glandular cell function in Sjögren's syndrome[J]. *JCI Insight*, 2020, 5(9): e133497.
- [18] KAKAN S S, JANGA S R, COOPERMAN B, et al. Small RNA deep sequencing identifies a unique miRNA signature released in serum exosomes in a mouse model of Sjögren's syndrome[J]. *Front Immunol*, 2020, 11: 1475.
- [19] LI F X, LIU Z W, ZHANG B, et al. Circular RNA sequencing indicates circ-IQGAP2 and circ-ZC₃H₆ as noninvasive biomarkers of primary Sjögren's syndrome[J]. *Rheumatology*, 2020, 59(9): 2603-2615.
- [20] HUANG D F, SHEN H B, XIE F F, et al. Role of mesenchymal stem cell-derived exosomes in the regeneration of different tissues [J]. *J Biol Eng*, 2024, 18(1): 36.
- [21] HU X L, ZHONG Y Q, KONG Y Y, et al. Lineage-specific exosomes promote the odontogenic differentiation of human dental pulp stem cells (DPSCs) through TGFβ1/smads signaling pathway *via* transfer of microRNAs[J]. *Stem Cell Res Ther*, 2019, 10(1): 170.
- [22] SWANSON W B, GONG T, ZHANG Z, et al. Controlled release of odontogenic exosomes from a biodegradable vehicle mediates dentinogenesis as a novel biomimetic pulp capping therapy[J]. *J Control Release*, 2020, 324: 679-694.
- [23] ZHUANG X Y, JI L L, JIANG H, et al. Exosomes derived from stem cells from the apical papilla promote dentine-pulp complex regeneration by inducing specific dentinogenesis [J]. *Stem Cells Int*, 2020, 2020: 5816723.
- [24] ZOU J Y, XIA H, JIANG Q Z, et al. Exosomes derived from odontogenic stem cells: Its role in the dentin-pulp complex [J]. *Regen Ther*, 2023, 24: 135-146.
- [25] GAO Y K, YUAN Z Y, YUAN X J, et al. Bioinspired porous microspheres for sustained hypoxic exosomes release and vascularized bone regeneration [J]. *Bioact Mater*, 2022, 14: 377-388.
- [26] KANG Y, XU C, MENG L A, et al. Exosome-functionalized magnesium-organic framework-based scaffolds with osteogenic, angiogenic and anti-inflammatory properties for accelerated bone regeneration[J]. *Bioact Mater*, 2022, 18: 26-41.
- [27] ZHANG Y, CHEN J Y, FU H J, 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.
- [28] CHEW J R J, CHUAH S J, TEO K Y W, et al. Mesenchymal stem cell exosomes enhance periodontal ligament cell functions and promote periodontal regeneration[J]. *Acta Biomater*, 2019, 89: 252-264.
- [29] WU J Y, CHEN L L, WANG R F, et al. Exosomes secreted by stem cells from human exfoliated deciduous teeth promote alveolar bone defect repair through the regulation of angiogenesis and osteogenesis [J]. *ACS Biomater Sci Eng*, 2019, 5(7): 3561-3571.
- [30] LIU A Q, LIN D, ZHAO H J, et al. Optimized BMSC-derived osteoinductive exosomes immobilized in hierarchical scaffold *via* lyophilization for bone repair through Bmpr2/Acvr2b competitive receptor-activated

- Smad pathway[J]. *Biomaterials*, 2021, 272: 120718.
- [31] ZHANG J Y, LIU X L, LI H Y, et al. Exosomes/tricalcium phosphate combination scaffolds can enhance bone regeneration by activating the PI3K/Akt signaling pathway[J]. *Stem Cell Res Ther*, 2016, 7(1): 136.
- [32] LIU L, GUO S J, SHI W 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.
- [33] LI R, LI D Z, WANG H N, et al. Exosomes from adipose-derived stem cells regulate M1/M2 macrophage phenotypic polarization to promote bone healing *via* miR-451a/MIF[J]. *Stem Cell Res Ther*, 2022, 13(1): 149.
- [34] WANG X D, ZHANG J N, GAN Y H, et al. Current understanding of pathogenesis and treatment of TMJ osteoarthritis[J]. *J Dent Res*, 2015, 94(5): 666-673.
- [35] LUO P, JIANG C, JI P, et al. Exosomes of stem cells from human exfoliated deciduous teeth as an anti-inflammatory agent in temporomandibular joint chondrocytes *via* miR-100-5p/mTOR [J]. *Stem Cell Res Ther*, 2019, 10(1): 216.
- [36] ZHANG S P, TEO K Y W, CHUAH S J, et al. MSC exosomes alleviate temporomandibular joint osteoarthritis by attenuating inflammation and restoring matrix homeostasis[J]. *Biomaterials*, 2019, 200: 35-47.
- [37] HU S L, CHEN B, ZHOU J N, et al. Dental pulp stem cell-derived exosomes revitalize salivary gland epithelial cell function in NOD mice *via* the GPER-mediated cAMP/PKA/CREB signaling pathway [J]. *J Transl Med*, 2023, 21(1): 361.
- [38] XIAO X Y, ZHANG N N, LONG Y Z, et al. Repair mechanism of radiation-induced salivary gland injury by hypoxia-pretreated human urine-derived stem cell exosomes[J]. *Oral Dis*, 2024, 30(3): 1234-1241.
- [39] LI G Y, ZHANG S Y, ZOU Y T, et al. The therapeutic potential of exosomes in immunotherapy[J]. *Front Immunol*, 2024, 15: 1424081.
- [40] LU Y, ZHENG J R, LIN P, et al. Tumor microenvironment-derived exosomes: a double-edged sword for advanced T cell-based immunotherapy [J]. *ACS Nano*, 2024, 18(40): 27230-27260.
- [41] WANG B L, CHENG D A, MA D Y, et al. Mutual regulation of PD-L1 immunosuppression between tumor-associated macrophages and tumor cells: a critical role for exosomes [J]. *Cell Commun Signal*, 2024, 22(1): 21.
- [42] PANG X, WANG S S, ZHANG M, et al. OSCC cell-secreted exosomal CMTM6 induced M2-like macrophages polarization *via* ERK1/2 signaling pathway[J]. *Cancer Immunol Immunother*, 2021, 70(4): 1015-1029.
- [43] LYU C, SUN H F, SUN Z Q, et al. Roles of exosomes in immunotherapy for solid cancers [J]. *Cell Death Dis*, 2024, 15: 106.
- [44] XIE C, DU L Y, GUO F Y, et al. Exosomes derived from microRNA-101-3p-overexpressing human bone marrow mesenchymal stem cells suppress oral cancer cell proliferation, invasion, and migration [J]. *Mol Cell Biochem*, 2019, 458(1): 11-26.
- [45] LIU P P, ZHANG Q, MI J, et al. Exosomes derived from stem cells of human deciduous exfoliated teeth inhibit angiogenesis *in vivo* and *in vitro* *via* the transfer of miR-100-5p and miR-1246[J]. *Stem Cell Res Ther*, 2022, 13(1): 89.
- [46] ZHAO W Z, LI K X, LI L B, et al. Mesenchymal stem cell-derived exosomes as drug delivery vehicles in disease therapy[J]. *Int J Mol Sci*, 2024, 25(14): 7715.
- [47] NOURI Z, BARFAR A, PERSEH S, et al. Exosomes as therapeutic and drug delivery vehicle for neurodegenerative diseases[J]. *J Nanobiotechnol*, 2024, 22(1): 463.
- [48] PANG J L, SHAO H, XU X G, et al. Targeted drug delivery of engineered mesenchymal stem/stromal-cell-derived exosomes in cardiovascular disease: recent trends and future perspectives [J]. *Front Bioeng Biotechnol*, 2024, 12: 1363742.
- [49] SHAO J T, ZARO J, SHEN Y X. Advances in exosome-based drug delivery and tumor targeting: From tissue distribution to intracellular fate [J]. *Int J Nanomed*, 2020, 15: 9355-9371.
- [50] CUI Y, HONG S B, XIA Y H, et al. Melatonin engineering M2 macrophage-derived exosomes mediate endoplasmic reticulum stress and immune reprogramming for periodontitis therapy [J]. *Adv Sci*, 2023, 10(27): 2302029.
- [51] DENG W, MENG Y, WANG B, et al. *In vitro* experimental study on the formation of microRNA-34a loaded exosomes and their inhibitory effect in oral squamous cell carcinoma[J]. *Cell Cycle*, 2022, 21(16): 1775-1783.
- [52] BATRAKOVA E V, KIM M S. Using exosomes, naturally-equipped nanocarriers, for drug delivery[J]. *J Control Release*, 2015, 219: 396-405.
- [53] ZENG H F, GUO S S, REN X C, et al. Current strategies for exosome cargo loading and targeting delivery[J]. *Cells*, 2023, 12(10): 1416.

-
- [54] HUANG C C, KANG M Y, LU Y, et al. Functionally engineered extracellular vesicles improve bone regeneration[J]. *Acta Biomater*, 2020, 109: 182-194.
- [55] LIANG Y J, DUAN L, LU J P, et al. Engineering exosomes for targeted drug delivery [J]. *Theranostics*, 2021, 11(7): 3183-3195.
- [56] DILSIZ N. A comprehensive review on recent advances in exosome isolation and characterization: Toward clinical applications [J]. *Transl Oncol*, 2024, 50: 102121.
- [57] NING X E, LIU R, HUANG Y Y, et al. Dental stem cell-derived exosomes: A review of their isolation, classification, functions, and mechanisms [J]. *Stem Cells Int*, 2024, 2024: 2187392.
- [58] HUDA M N, NAFIUJJAMAN M, DEAGUERO I G, et al. Potential use of exosomes as diagnostic biomarkers and in targeted drug delivery: Progress in clinical and preclinical applications [J]. *ACS Biomater Sci Eng*, 2021, 7(6): 2106-2149.
- [59] LIU X J, LIU C, LIN Q Q, et al. Exosome-loaded hydrogels for craniofacial bone tissue regeneration [J]. *Biomed Mater*, 2024, 19(5): 052002.
- [60] LEI F Z, LI M J, LIN T T, et al. Treatment of inflammatory bone loss in periodontitis by stem cell-derived exosomes [J]. *Acta Biomater*, 2022, 141: 333-343.