[DOI]10.12016/j.issn.2096-1456.202550516

·综述·

细菌胞外囊泡在龋病和牙周病中的研究进展

陈佳琪[1]，　杨佼佼[2]，　李继遥[1]

1.口腔疾病防治全国重点实验室 国家口腔医学中心 口腔疾病国家临床医学研究中心 四川大学华西口腔医院牙体牙髓病科，四川 成都（610041）；　2.口腔疾病防治全国重点实验室 国家口腔医学中心 口腔疾病国家临床医学研究中心，四川 成都（610041）

【摘要】 细菌胞外囊泡（BEVs）是细菌主动或被动释放的、由磷脂双分子膜包裹的纳米级囊泡，携带蛋白质、核酸及脂质等多种生物活性物质，能够在微生物群落与宿主之间介导信息传递。近年来研究表明，BEVs在龋病与牙周病的发生发展中发挥重要作用：在龋病中，变异链球菌等致龋菌来源的BEVs可促进生物膜形成与成熟，增强酸性微环境，加剧牙体组织脱矿；在牙周病中，牙龈卟啉单胞菌、具核梭杆菌等致病菌来源的BEVs可损伤黏膜屏障，诱导炎症反应并推动骨吸收相关通路激活，从而促进牙周组织破坏。基于其可检测性，BEVs在唾液、菌斑及龈沟液等口腔样本中具有作为诊断标志物的潜力，同时也为靶向干预提供新的治疗思路。此外，部分研究提示口腔来源BEVs可能通过“口腔—全身轴”参与远端炎症放大过程，本文在聚焦BEVs对龋病与牙周病局部致病机制的基础上对其潜在系统影响作拓展性概述。总体而言，BEVs有望为龋病与牙周病的机制研究及精准防治提供新的理论依据与转化方向。

【关键词】 细菌胞外囊泡；　变异链球菌；　牙龈卟啉单胞菌；　具核梭杆菌；　龋病；　牙周病；　口腔—全身轴

【中图分类号】 R78　【文献标志码】 A　【文章编号】 2096-1456（2026）09-0895-11

【引用著录格式】 陈佳琪，杨佼佼，李继遥. 细菌胞外囊泡在龋病和牙周病中的研究进展[J]. 口腔疾病防治，2026, 34(9): 895-905. doi:10.12016/j.issn.2096-1456.202550516.

微信公众号

Research progress on bacterial extracellular vesicles in dental caries and periodontal disease

CHEN Jiaqi[1], YANG Jiaojiao[2], LI Jiyao[1]. 1. State Key Laboratory of Oral Diseases & National Center for Stomatology & National Clinical Research Center for Oral Diseases & Department of Operative Dentistry and Endodontics, West China Hospital of Stomatology, Sichuan University, Chengdu 610041, China;　2. State Key Laboratory of Oral Diseases & National Center for Stomatology & National Clinical Research Center for Oral Diseases, Chengdu 610041, China

Corresponding author: LI Jiyao, Email: jiyaoliscu@163.com

【Abstract】 Bacterial extracellular vesicles (BEVs) are nanoscale, lipid bilayer - enclosed vesicles that are actively or passively released by bacteria. They carry diverse bioactive cargos, including proteins, nucleic acids, and lipids, and mediate information exchange between microbial communities and hosts. Increasing evidence indicates that BEVs play important roles in the initiation and progression of dental caries and periodontitis. In dental caries, BEVs derived from cariogenic bacteria such as *Streptococcus mutans* can promote biofilm formation and maturation, enhance the acidic microenvironment, and exacerbate demineralization of dental hard tissues. In periodontitis, BEVs released by key periodontal pathogens, including *Porphyromonas gingivalis* and *Fusobacterium nucleatum*, may disrupt the mucosal barrier, trigger inflammatory responses, and activate bone resorption - related pathways, thereby promoting periodontal tissue destruction. Owing to their detectability, BEVs in oral samples such as saliva, dental plaque, and gingival crevicular fluid show promise as diagnostic biomarkers and also provide new therapeutic opportunities for targeted interventions.

【收稿日期】2025-11-11；　【修回日期】2026-02-13

【基金项目】国家自然科学基金项目（81991501）

【作者简介】陈佳琪，硕士研究生在读，Email：chenjiaqi0225@163.com

【通信作者】李继遥，教授，博士，Email：jiyaoliscu@163.com

In addition, emerging studies suggest that oral BEVs may contribute to distal inflammatory amplification through an "oral - systemic axis"; therefore, while focusing on the local pathogenic mechanisms of BEVs in dental caries and periodontitis, this review also briefly outlines their potential systemic implications as an extension. Overall, BEVs may offer novel mechanistic insights and translational directions to support precise prevention and management of dental caries and periodontitis.

【Key words】 bacterial extracellular vesicles; *Streptococcus mutans*; *Porphyromonas gingivalis*; *Fusobacterium nucleatum*; dental caries; periodontal disease; oral-systemic axis

J Prev Treat Stomatol Dis, 2026, 34(9): 895-905.

口腔健康对全身健康至关重要。龋病与牙周病是两种常见的慢性细菌性感染性疾病，除直接损害牙齿及其支持组织外，也与多种系统性疾病相关[1-2]。变异链球菌（*Streptococcus mutans*）是龋病的核心致病菌，牙龈卟啉单胞菌（*Porphyromonas gingivalis*）和具核梭杆菌（*Fusobacterium nucleatum*）则是牙周病的重要致病菌。变异链球菌通过黏附牙面、参与生物膜形成并产酸诱发牙体硬组织脱矿[3]；牙龈卟啉单胞菌与具核梭杆菌可通过龈下定植推动局部慢性炎症反应与骨吸收，从而导致牙周支持组织破坏[4-5]。除直接释放毒力因子外，越来越多研究显示，口腔致病菌还可通过释放细菌胞外囊泡（bacterial extracellular vesicles，BEVs）实现毒力因子的"打包式"递送[6]与跨距离传播[7-8]。BEVs为由磷脂双分子层包裹的纳米级囊泡，可携带蛋白质、脂多糖（lipopolysaccharide，LPS）、毒力酶及小RNA等活性成分，在口腔复杂微环境中相对稳定存在，并通过增强菌群互作、促进生物膜构建、激活免疫炎症通路等方式放大龋病与牙周病的局部致病效应[9]。此外，部分研究提示口腔微生物因素可通过口腔—全身轴与系统性疾病发生发展存在关联[10-11]，而BEVs可能是其中参与远端效应的重要介质之一[12-13]。因此，本文将聚焦口腔局部疾病层面，系统综述BEVs在龋病与牙周病中的组成特征、致病机制及其作为诊断标志物与潜在治疗靶点的研究进展，并对其可能的全身影响作简要的拓展性概述。

1　细菌胞外囊泡的定义与致病机制

1.1　细菌胞外囊泡定义

细菌胞外囊泡（bacterial extracellular vesicles，BEVs）是细菌主动或被动释放的、由磷脂双分子膜包裹的纳米级囊泡。革兰氏阴性菌来源的胞外囊泡被称为外膜囊泡（outer membrane vesicles，OMVs），由外膜向外出芽形成；革兰阳性菌虽没有外膜，但也能释放膜囊泡（membrane vesicles，MVs/EVs），其包膜源自细胞质膜并常含细胞壁成分。两类囊泡均可携带蛋白、脂质、核酸与代谢物，并介导菌群与宿主之间的相互作用。

1.2　细菌胞外囊泡生成

以牙龈卟啉单胞菌、具核梭杆菌等为例的革兰氏阴性菌，它们的外膜囊泡通常经由外膜局灶性出芽并缢断形成，这一过程受脂多糖或脂质A结构[14-15]、外膜—肽聚糖的联结程度、周质应激以及膜张力等因素的共同调控。相比之下，变异链球菌等革兰阳性菌的肽聚糖层较厚，膜囊泡的生成与自溶素介导的细胞壁重塑以及膜去极化或应激反应密切相关。已有研究表明，变异链球菌的自溶素参与外膜囊泡生物生成的调控[16]，自溶素通过水解细胞壁中的肽聚糖，增加细胞壁通透性，形成孔隙，从而促进胞质膜或膜片段的脱出，生成膜囊泡。

1.3　细菌胞外囊泡组成

细菌胞外囊泡的组成包括其膜结构和内容物。

胞外囊泡的膜主要由外膜磷脂双层组成，其中含有脂多糖、磷脂质和外膜蛋白等分子。脂多糖位于膜的外层，是细菌与宿主免疫系统相互作用的关键分子，有助于细菌的免疫逃逸和致病性表达[17]。外膜蛋白包括载体蛋白、酶类和黏附因子，参与囊泡的形成、细菌与宿主细胞的结合以及毒力因子的传递。外膜磷脂双层不仅提供物理屏障，还参与细菌与宿主环境的相互作用，对细菌的生存和感染能力至关重要。

胞外囊泡的内容物 包括蛋白质、脂质、核酸以及其他生物分子，如毒素和酶。以口腔致病菌为例，牙龈卟啉单胞菌外膜囊泡通常富集脂多糖、蛋白酶、卟啉酰胺水解酶（peptidyl-prolylcis-trans isom-

erase，PPAD）及多种黏附因子[18]；具核梭杆菌外膜囊泡则携带黏附素、毒力相关酶与小RNA，其囊泡可通过影响宿主免疫细胞代谢状态调节免疫应答，并形成免疫抑制倾向[13]；而在变异链球菌膜囊泡中，常检测到葡萄糖转移酶（glucosyltransferase，Gtf）、胞外DNA与小RNA[19]，这些成分有助于变异链球菌实现跨菌种通讯并维持生物膜稳态。

1.4　细菌胞外囊泡作用机制

细菌胞外囊泡通过黏附与递送、促进免疫逃逸与炎症放大以及穿越细胞屏障这三种机制，调控宿主免疫反应，促进细菌的定植和致病过程（图1）。

1.4.1　黏附与递送　细菌胞外囊泡表面的脂多糖与外膜蛋白介导其对上皮与免疫细胞的黏附、摄取与胞内转运[20]，从而在无需菌体扩增的前提下，定向递送毒力因子与小RNA[21]，远距调控宿主固有与适应性免疫通路。研究发现，脆弱拟杆菌（*Bacteroides fragilis*）胞外囊泡中释放荚膜多糖A抗原，刺激Toll样受体2，导致树突状细胞产生Gadd45，进而产生白细胞介素-10（interleukin-10，IL-10），促进调节性T细胞的发育[22]。另有研究发现，双歧杆菌（*Bifidobacterium*）来源的胞外囊泡通过动力蛋白依赖性内吞作用被肺癌细胞摄取，并通过Toll样受体4的核因子κB（nuclear factor kappa-B，NF-κB）通路上调程序性死亡配体-1（programmed death-ligand 1，PD-L1）的表达[23]，促使肿瘤能够逃避宿主免疫监视。

1.4.2　免疫逃逸与炎症放大　细菌胞外囊泡可削弱补体级联与中性粒细胞吞噬作用[15]，重塑巨噬细胞极化状态，诱导促炎细胞因子的释放，从而在局部微环境中形成免疫耐受，促进炎症反应的持续和加剧[24]。研究发现，具核梭杆菌的外膜囊泡可以引起色氨酸向犬尿氨酸通路的代谢重编程，进而抑制抗肿瘤免疫，并与免疫治疗耐受性相关[13]。

1.4.3　穿越细胞屏障　细菌胞外囊泡通过裂解、重塑紧密连接与黏附连接[25]，扰动上皮稳态并提升屏障通透性[26]，促进毒力因子与炎性信号的跨屏障转运，从而推动远端组织的炎症放大与细菌定植。

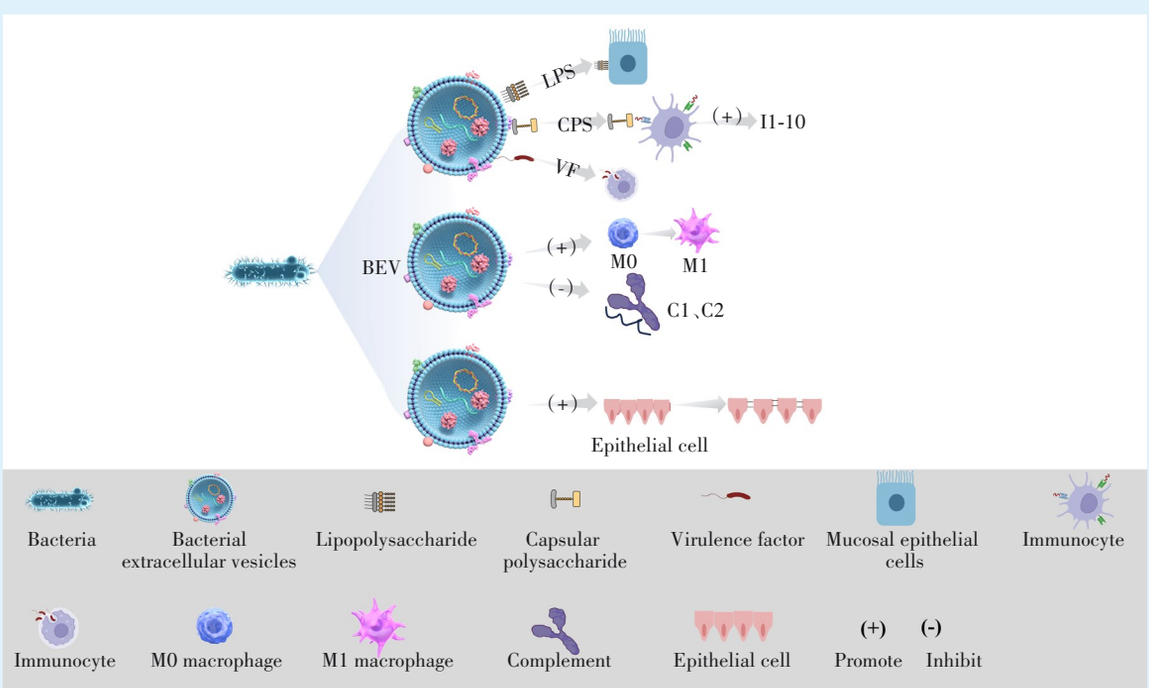

Figure was created with Microsoft PowerPonit 2010. BEV: bacterial extracellular vesicle; LPS: lipopolysaccharide; CPS: capsular polysaccharide; VF: virulence factor; M0: naive macrophage; M1: classically activated macrophage; IL-10: interleukin-10

Figure 1　Bacterial extracellular vesicles regulate immune responses and promote infection *via* adhesion, immune evasion, and barrier crossing

图1　细菌胞外囊泡通过黏附、免疫逃逸和穿越屏障机制调控免疫反应，促进感染

2　细菌膜外囊泡在口腔局部微生态中的“促病作用”

2.1　龋病

龋病的发生发展与生物膜形成、胞外基质累积及酸性代谢产物滞留密切相关。研究显示，变异链球菌来源膜囊泡可作为致龋因子的“打包单元”，其所携带的葡萄糖基转移酶（Gtf）能够催生不溶性葡聚糖并促进基质形成[27]；囊泡伴随释放的胞外DNA（extracellular DNA，eDNA）及小RNA等核酸成分可增强早期黏附、提高基质网格致密度并强化扩散屏障，从而促进酸性微环境维持并加剧脱矿[28-29]。

在菌群互作层面，变异链球菌来源膜囊泡中含有的Gtf可吸附至异种微生物表面并促进多菌种基质共建[30]，增强与白念珠菌等共致病体的结构耦联，进一步提升生物膜稳定性与致龋性[31]。与此同时，囊泡内核酸作为跨菌种通讯信号[32]，可能参与调控生物膜群落组成与稳态维持，进一步放大龋病环境中的微生态失衡，加剧酸损伤。

除促进多菌种黏附与基质共建外，变异链球菌膜囊泡还可作为细胞外DNA的重要载体，在生物膜早期形成结构化“DNA纤维网络”，并与Gtf介导的葡聚糖基质协同增强牙面黏附与微菌落稳定性，从而加速脱矿过程[33]。在宿主反应层面，研究提示其囊泡可驱动巨噬细胞炎性小体相关反应并伴随代谢表型转变，促进促炎因子释放，提示膜囊泡除“建膜”外亦可能通过炎症放大参与龋病向深部组织进展的风险环节[34]。

值得注意的是，变异链球菌膜囊泡的产生与内容物装载受环境pH与应激状态影响。酸性条件下囊泡的理化性质及Gtf相关活性可发生改变[27]，并伴随与耐酸相关蛋白/核酸的富集，从而增强菌体在低pH环境中的适应性并维持致龋优势[35]。因此，从“囊泡生成—内容物—致龋表型”角度来系统解析其关键分子，有助于更精准地理解囊泡在龋病中的致病机制，并为靶向干预提供依据。

2.2　牙周病

牙周病的发生和进展是一个复杂的过程，通常始于口腔内细菌群落的失调和局部免疫反应的改变。细菌通过附着在牙龈表面并形成生物膜，导致牙龈炎症反应的加剧。随着疾病的进展，细菌通过分泌各种致病因子破坏口腔上皮屏障，增加局部组织的通透性，促进免疫逃逸，甚至影响骨代谢，引发牙槽骨的吸收。细菌的膜囊泡在这一过程中作为细菌与宿主细胞相互作用的媒介，能够携带多种致病因子并直接作用于牙周组织。

牙龈卟啉单胞菌外膜囊泡通过携带蛋白酶等致病因子，裂解上皮细胞之间的紧密连接分子[36]，从而破坏上皮屏障，增加局部组织的通透性，为致病菌和其他炎症因子深入组织创造条件。此外，牙龈卟啉单胞菌外膜囊泡携带的蛋白酶[37]还能降解免疫系统的关键分子[38]，从而扰乱免疫清除机制。由于牙龈卟啉单胞菌外膜囊泡中的脂质A在结构上高度可变，通过脂质A结构的变化，可以表现为激活免疫的弱激动剂[39]或抑制免疫的拮抗剂[40]，能够通过不同的受体激活免疫反应[41]，这种免疫反应的调节有助于牙龈卟啉单胞菌在局部环境中的免疫逃逸[42-43]，使其能够在牙周组织中持续生长和侵袭。进一步地，牙龈卟啉单胞菌外膜囊泡通过Toll样受体-4（Toll-like receptor 4，TLR4）/MyD88/NF-κB等信号通路[44]诱导炎症因子的释放，促进破骨细胞的活化[45]，并上调破骨相关的信号分子，直接推动牙槽骨的吸收，同时抑制成骨分化[46]，推动骨代谢失衡，最终加剧牙周病的发生和进展。

具核梭杆菌外膜囊泡通过其携带的黏附素家族[5]和其他毒力因子[12]，在口腔内发挥重要的致病作用。它们不仅促进了具核梭杆菌与口腔内其他细菌以及宿主细胞的稳定结合，还增强了多菌种生物膜的结构与稳定性[47]，为局部病原体的生长提供了有利环境。此外，具核梭杆菌外膜囊泡能够通过诱导细胞的吞噬作用[48]，促使细菌跨越口腔上皮屏障[49]，进入更深层的组织。这一过程增强了具核梭杆菌在局部感染区域的扩展能力，为组织的进一步侵袭和损伤创造了条件。在免疫层面，具核梭杆菌外膜囊泡通过激活Toll样受体并诱导NF-κB通路，进一步激活炎性小体，释放白细胞介素-1β（interleukin-1β，IL-1β）等促炎因子[50-51]，导致局部炎症反应加剧，从而推动牙龈和牙槽骨的破坏。此外，其外膜囊泡还可能通过改变免疫细胞的功能，干扰宿主的免疫防御系统[52-53]，促进局部感染的持续性。这些特征使得具核梭杆菌在牙周病病理过程中扮演了重要角色，促进了牙周疾病的发生和发展。

除上述两类代表性菌种外，牙周炎相关的其他革兰氏阴性菌亦可通过外膜囊泡参与病程。例如，伴放线聚集杆菌外膜囊泡可携带白细胞毒素

等效应分子，并呈现明显的囊泡异质性，使其能在局部微环境中实现“定向递送”并进一步损伤免疫细胞[54-55]。此外，红色复合体成员的囊泡在脂蛋白、蛋白酶与核酸等囊泡内容物上与牙龈卟啉单胞菌存在差异，能够诱导不同的模式识别受体响应，并在巨噬细胞中提供炎性小体的激活信号，从而影响炎症类型与持续性[56-57]。这些证据提示，牙周囊泡效应并非单菌决定，而与菌群结构及囊泡内容物异质性密切相关。

2.3　龋病*vs.*牙周病：囊泡驱动的异同

在口腔疾病谱系中，龋病与牙周病致病菌产生的胞外囊泡致病机制共同点在于：细菌均以“纳米级囊泡”形态实现远距递送[8]与群落协同，但在内容物与组织结局上呈现出清晰差异：前者以Gtf与eDNA为核心[19]，增强早期黏附与基质致密度，形成扩散屏障，促进酸滞留[27, 31]，促进牙釉质与牙本质脱矿过程；后者则以牙龈上皮结缔组织与牙槽骨为主要靶区，一方面破坏紧密连接与细胞外基质[36, 49]、削弱屏障并促进组织侵袭，另一方面通过调节宿主的免疫代谢[37]驱动破骨与骨吸收[50-51]。群落生态学上，变异链球菌外膜囊泡更像“结构与代谢放大器”，维持酸发生与潴留的优势；而牙龈卟啉单胞菌和具核梭杆菌的外膜囊泡则充当“菌群工程师”，重塑屏障网络并外溢炎性生态位（表1）。

表1　主要口腔致病菌来源细胞外囊泡的异质性比较

Table 1　Heterogeneity of bacterial extracellular vesicle derived from major oral pathogens

Pathogen type	Typical size range*	Main membrane features	Representative cargo	Functional characteristics
Streptococcus mutans membrane vesicles	Mostly 50 – 250 nm[27]	Derived from the cytoplasmic membrane; peptidoglycan fragments and surface proteins can be present; vesicle production increases under acidic stress[27]	Glucosyltransferases, extracellular DNA, small RNAs, acid-tolerance – related proteins[27-28]	Enhance initial adhesion and biofilm matrix density; create diffusion barriers that trap acids; act as “structural and metabolic amplifiers” of caries progression[29, 31]
Porphyromonas gingivalis outer membrane vesicles	Mostly 50 – 300 nm[36]	Formed by outer-membrane budding; enriched in lipid A and numerous outer-membrane proteins[46]	Gingipains, hemagglutinins, adhesins, lipid A, small RNAs[58-59]	Disrupt epithelial barriers, reprogram immune responses, promote osteoclastogenesis and bone loss; contribute to systemic diseases[60-61] (Alzheimer’s, atherosclerosis, metabolic disorders)
Fusobacterium nucleatum outer membrane vesicles	Mostly 50 – 200 nm[12]	Contain lipopolysaccharide, outer-membrane proteins, and characteristic adhesins binding to host and bacterial receptors[47]	Adhesins, proteases, pro-inflammatory factors, small RNAs, tryptophan-metabolism enzymes[48-49]	Promote multispecies biofilms, increase epithelial permeability, activate NF-κB/inflammasome pathways[43-44]; linked to periodontitis and colorectal-cancer-associated dysbiosis[7, 13]

* Size ranges are approximate and vary with isolation and measurement methods

2.4　其他细菌胞外囊泡相关口腔疾病

除龋病与牙周病外，现有研究亦提示BEVs可能参与其他口腔细菌相关疾病的炎症放大与组织破坏，但总体证据仍以体外与动物实验为主且研究数量有限。例如，在根尖周炎中，部分优势菌（如粪肠球菌）来源囊泡可富集毒力与炎症相关分子，促进破骨相关反应并加重根尖周骨质破坏[62-63]；在种植体周围炎环境下，生物膜来源囊泡可能促进钛表面生物膜成熟并上调上皮炎症因子表达，从而影响周围软硬组织微环境[64-65]；对于急性牙源性感染及间隙感染等，囊泡通过在炎症级联、屏障损伤与菌群协同扩散中的作用，可能参与病灶扩展过程[66-67]。

3　细菌胞外囊泡在口腔相关联的系统性疾病中的“远端作用”

尽管本文重点讨论BEVs在龋病与牙周病局部过程中的作用，但据近年来有关“口腔—全身轴”的相关研究提示，口腔致病菌来源囊泡可能通过进入血液循环或胃肠道途径[68]，在远端组织触发或放大炎症反应。现有证据中，牙龈卟啉单胞菌外膜囊泡被报道可跨越血脑屏障并诱导神经炎

症，从而与神经退行性改变相关[69-70]；具核梭杆菌外膜囊泡与类风湿性关节炎的炎症放大存在关联线索[71-72]；此外，牙周致病菌囊泡进入胰岛素靶器官并干扰代谢信号的研究，也为牙周炎与糖代谢异常的联系提供了可检验的机制路径[73-74]。

部分基础与临床研究提示口腔致病菌及其胞外囊泡可能参与某些肿瘤微环境的重塑[7]及参与肠道炎症性疾病的复发[75]，但现有证据仍较为有限且异质性较大，未来有待进一步深入研究。

此外，现有研究主要基于体外实验和动物模型，提示细菌来源的胞外囊泡在口腔局部及全身系统性疾病中更多地充当介导者和放大器，而非单一或决定性的致病因素。现阶段尚难以与菌体本身、游离毒素及其他危险因素进行直接比较，未来需要结合大型队列、多组学分析和功能阻断实验，进一步明确其在口腔相关系统性疾病中的作用。

4　靶向治疗与应用前景

4.1　细菌胞外囊泡作为诊断标志物

在龋病与牙周病的无创监测中，BEVs具有“可检测、可分型、可动态追踪”的优势。口腔样本获取便捷，唾液、菌斑与龈沟液可作为优先检测样本[76]；通过解析不同菌源BEVs的丰度变化及其代表性内容物（如变异链球菌相关的Gtf、牙龈卟啉单胞菌蛋白酶与脂质A、具核梭杆菌黏附素等），有望实现对龋病活跃度、生物膜致病性以及牙周炎症负荷的分层评估。此外，部分研究亦提示口腔囊泡相关核酸标志物可用于牙周病合并代谢异常的风险提示与随访[77-78]。未来需要在标准化分离鉴定与质控框架下，开展多中心队列验证与阈值构建，以提升其临床可用性。

4.2　细菌胞外囊泡作为治疗靶点

围绕龋病与牙周病的靶向干预，可将“囊泡—致病模块”作为可操作的治疗切入点。其一，针对牙周致病菌外膜囊泡，可通过干扰外膜-肽聚糖联结、脂质A改构或干扰周质应激通路来抑制囊泡过量生成，从源头降低囊泡负荷[79]；其二，阻断囊泡与宿主的关键受体轴，利用中和分子或拮抗肽干预LPS-TLR等配体—受体互作，抑制下游炎症放大[80]；其三，在龋病中可进一步考虑靶向囊泡携带的基质构建因子（如Gtf相关活性）与eDNA介导的结构稳态，以削弱生物膜致密化与酸滞留过程；其四，采用“纳米海绵”等策略捕获并清除具有高炎症活性的囊泡，联合去毒化处理以降低反应原性[81]。总体而言，上述策略能够分别对应龋病的建膜与酸损伤过程以及牙周病的屏障破坏、免疫放大和骨吸收过程，从而为分层管理与组合式干预提供思路。

4.3　细菌胞外囊泡作为治疗载体

在载体化与递送方面，去毒化BEVs可作为口腔局部递送与免疫调控的平台。通过脂质A去磷酸化或敲除关键修饰酶可获得低毒性囊泡[82-83]，并可进一步装载抗炎miRNA/siRNA、抑制性肽或小分子药物以实现靶向调控[84]。考虑到口腔疾病的局部特征，给药策略宜优先采用可控释放与局部富集形式：例如牙周炎可使用龈袋凝胶、可降解膜或微针贴片实现持续递送[85-86]；龋病可结合涂布材料、缓释水凝胶或表面黏附型载体提高在牙面/菌斑中的驻留时间[87-88]。

此外，不同的囊泡提取方法在纯度、产率与批次稳定性上的差异较大。研究显示差速超速离心提取法产率高但蛋白污染多、批次间差异明显；密度梯度离心提取法纯度高但流程复杂且产率偏低；尺寸排阻色谱提取法在纯度和活性保持方面有优势，但对上样量与柱效高度敏感[89-90]。当前尚缺乏统一的质量控制标准，使BEVs作为治疗制剂的可重复性面临重要瓶颈。

4.4　技术局限性

目前口腔致病菌BEVs的研究多采用差速超速离心、密度梯度离心或尺寸排阻色谱等物理方法提取，但不同策略实际得到的囊泡群体并不完全相同，从而对其成分谱和功能读数产生系统性偏倚。差速超速离心法容易共沉淀高丰度可溶性蛋白、脂蛋白和细胞碎片，使某些炎症因子或代谢酶被误归为囊泡内容物[91]；密度梯度离心法则更偏向富集密度较高的亚群，可能低估小颗粒或低密度BEVs的贡献[90]；尺寸排阻色谱法则倾向根据粒径窗口筛选囊泡，可能在分离过程中弱化大型或表面粗糙囊泡的比例，使最终成分与功能更偏向特定粒径区间的亚群[89]。此外，在高黏度的唾液、龈沟液和菌斑样本中，预处理本身也会改变表面蛋白和凝集状态，进一步影响后续功能验证的结果[92]。因此，在解读不同研究间BEVs核心成分和生物学效应差异时，应充分考虑分离流程和前处理条件的差异，尽可能详细报告方法学细节，并结合多种表征手段（如电镜、标志蛋白检测）进行交叉验证[93]，以减少技术因素对生物学结论的干扰。

4.5　外泌体研究进展对BEVs研究的启示

近年来外泌体(exosomes)研究快速发展[94],其在组学解析、单囊泡分析与工程化改造方面形成了较为成熟的技术体系,可为BEVs的研究提供重要方法学借鉴。需要强调的是,外泌体通常指真核细胞来源的胞外囊泡亚型,主要通过多囊泡体(multivesicular bodies,MVBs)途径形成并释放;而BEVs为细菌释放的胞外囊泡,其生物发生机制与膜来源可随菌种而异,二者在概念与生物学属性上并不等同。由于来源与形成途径不同,外泌体与BEVs在关键属性上存在系统性差异,需要加以区分。外泌体是真核细胞经多囊泡体途径形成并释放的囊泡亚型,其膜与内容物主要反映宿主细胞来源特征;而BEVs由细菌释放,囊泡膜来源与形成机制会随菌种结构、生长状态及环境刺激而变化,并常呈现更鲜明的细菌特征性结构组分与功能分子谱,因此在先天免疫识别与炎症激活方面往往具有更突出的潜能,其安全性与免疫原性评估的关注点也与外泌体不同。与此同时,两者在鉴定与质控逻辑上亦不相同:外泌体领域已建立相对成熟的标志物与鉴定框架,而BEVs目前仍缺乏跨菌种通用的核心标志物组合,分离纯化与质量控制更需结合菌源性证据链、样本基质干扰以及潜在污染风险进行综合判断。因此,外泌体研究方法对BEVs具有重要借鉴意义,但应在明确概念边界与适配评价标准的前提下选择性迁移,避免直接套用。

外泌体研究的若干进展对BEVs研究具有启示意义。其一,高通量囊泡组学技术[95-96]推动了囊泡蛋白、RNA及脂质等内容物的系统性分析,该技术可用于构建龋病与牙周病相关菌源BEVs的“内容物图谱”,并与致病表型、宿主反应进行关联分析,从而提升机制研究的深度与可解释性。其二,单囊泡流式、超分辨成像等单囊泡分析方法有助于识别囊泡异质性并实现更精细的分群[97],这对解决BEVs研究中“不同菌种/不同生长状态/不同环境刺激下囊泡高度异质”的问题尤为关键,也有利于提高潜在诊断标志物的稳定性与重复性。其三,外泌体领域在工程化改造[98-99]与靶向递送方面的策略[100-101](如表面修饰、靶向配体构建及递送效率评价框架)已较为成熟,可为构建低毒性、高稳定性、具有口腔局部靶向能力的BEVs类递送系统提供可借鉴路径,但应同时重视BEVs的免疫原性与安全性评估体系建立。

总体而言,若能在充分区分概念与属性差异的前提下,将外泌体领域成熟技术与评价范式有选择地引入BEVs研究,有望在机制阐释、诊断标志物开发及载体化应用等方面进一步提升该领域的研究深度与转化潜力。

未来研究应进一步面向龋病与牙周病的临床问题建立可转化的“证据链”:一方面,需在样本采集、分离纯化、内容物鉴定与批次一致性方面形成可复现的标准与质控框架,以减少不同研究间方法学差异带来的系统性偏倚;另一方面,需将菌源BEVs的内容物与宿主受体轴、炎症/骨代谢结局进行因果验证,并在人群中开展前瞻性验证,从而推动BEVs相关诊断分层与靶向干预策略在口腔局部场景中的落地。

5　总结与展望

本文聚焦龋病与牙周病两类口腔常见慢性感染性疾病,综述了主要口腔致病菌来源BEVs的组成特征及其在生物膜构建、黏膜屏障损伤、免疫炎症放大与骨代谢失衡等环节中的关键作用,并总结了其在口腔样本诊断分层、靶向干预与工程化递送方面的潜在转化价值。总体而言,围绕菌源BEVs建立标准化鉴定与机制验证体系,将有望为龋病与牙周病的精准防治提供新的理论依据与技术路径。

【Author contributions】 Chen JQ conceptualized and wrote the article. Yang JJ collected the references, revised the article. Li JY conceptualized and reviewed the article. All authors read and approved the final manuscript as submitted.

【Ethics statement】 The authors have nothing to report.

【Funding】 This study was supported by the grants from National Natural Science Foundation of China (No. 81991501). The funder had no role in the study design, data collection and analysis, decision to publish, or preparation of the manuscript.

【Competing interests】 All authors have completed the ICMJE uniform disclosure form at www.icmje.org/disclosure-of-interest/ and declare: support from the National Natural Science Foundation of China; no financial relationships with any organisation that might have an interest in the submitted work; no other relationships or activities that could appear to have influenced the submitted work.

【Data availability statement】 Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

【Generative AI statement】 Figure in this manuscript was created with Microsoft PowerPonit 2010. The manuscript did not use generative AI software during the creative process, but ChatGDP 4.0 was used for text polishing. The authors reviewed and edited the output and take full

responsibility for the manuscript.

参考文献

[1] Pitts NB, Twetman S, Fisher J, et al. Understanding dental caries as a non-communicable disease[J]. Br Dent J, 2021, 231(12): 749-753. doi: 10.1038/s41415-021-3775-4.

[2] Senpuku H, Nakamura T, Iwabuchi Y, et al. Effects of complex DNA and MVs with GTF extracted from *Streptococcus mutans* on the oral biofilm[J]. Molecules, 2019, 24(17): 3131. doi: 10.3390/molecules24173131.

[3] Cho H, Ren Z, Divaris K, et al. *Selenomonas sputigena* acts as a pathobiont mediating spatial structure and biofilm virulence in early childhood caries[J]. Nat Commun, 2023, 14(1): 2919. doi: 10.1038/s41467-023-38346-3.

[4] Xu J, Yu L, Ye S, et al. Oral microbiota-host interaction: the chief culprit of alveolar bone resorption[J]. Front Immunol, 2024, 15: 1254516. doi: 10.3389/fimmu.2024.1254516.

[5] Zhang X, Cheng S, Chen S, et al. Periodontitis-associated *Fusobacterium nucleatum* promotes ulcerative colitis by ferroptosis-mediated gut barrier disruption[J]. NPJ Biofilms Microbiomes, 2025, 11(1): 155. doi: 10.1038/s41522-025-00763-1.

[6] Kim TL, Oh SY, Lee KY, et al. *Streptococcus mutans*-derived extracellular vesicles promote herpes simplex virus infection in oral epithelia[J]. Virulence, 2026, 17(1): 2602261. doi: 10.1080/21505594.2025.2602261.

[7] Zheng X, Gong T, Luo W, et al. *Fusobacterium nucleatum* extracellular vesicles are enriched in colorectal cancer and facilitate bacterial adhesion[J]. Sci Adv, 2024, 10(38): eado0016. doi: 10.1126/sciadv.ado0016.

[8] Liu H, Zhang H, Han Y, et al. Bacterial extracellular vesicles-based therapeutic strategies for bone and soft tissue tumors therapy[J]. Theranostics, 2022, 12(15): 6576-6594. doi: 10.7150/thno.78034.

[9] Toyofuku M, Schild S, Kaparakis-Liaskos M, et al. Composition and functions of bacterial membrane vesicles[J]. Nat Rev Microbiol, 2023, 21(7): 415-430. doi: 10.1038/s41579-023-00875-5.

[10] Botelho J, Mascarenhas P, Viana J, et al. An umbrella review of the evidence linking oral health and systemic noncommunicable diseases[J]. Nat Commun, 2022, 13(1): 7614. doi: 10.1038/s41467-022-35337-8.

[11] Abe T, Tominaga K, Saito H, et al. Effect of oral health on functional disability and mortality in older adults in Japan: a cohort study[J]. Lancet Healthy Longev, 2024, 5(11): 100636. doi: 10.1016/j.lanhl.2024.08.005.

[12] Zhang L, Zhang D, Liu C, et al. Outer membrane vesicles derived from *Fusobacterium nucleatum* trigger periodontitis through host overimmunity[J]. Adv Sci (Weinh), 2024, 11(47): 2400882. doi: 10.1002/advs.202400882.

[13] Li W, Zhang Z, Wu R, et al. *Fusobacterium nucleatum*-derived outer membrane vesicles promote immunotherapy resistance *via* changes in tryptophan metabolism in tumour-associated macrophages[J]. J Extracell Vesicles, 2025, 14(4): e70070. doi: 10.1002/jev2.70070.

[14] De Langhe N, Van Dorpe S, Guilbert N, et al. Mapping bacterial extracellular vesicle research: insights, best practices and knowledge gaps[J]. Nat Commun, 2024, 15(1): 9410. doi: 10.1038/s41467-024-53279-1.

[15] Dehinwal R, Gopinath T, Smith RD, et al. A pH-sensitive motif in an outer membrane protein activates bacterial membrane vesicle production[J]. Nat Commun, 2024, 15(1): 6958. doi: 10.1038/s41467-024-51364-z.

[16] Nagasawa R, Ito T, Yamamoto C, et al. Membrane vesicle production *via* cell-to-cell communication-induced autolysis in *Streptococcus mutans*[J]. Microbiol Spectr, 2025, 13(7): e0033425. doi: 10.1128/spectrum.00334-25.

[17] Jaishankar J, Yang H, O'Keefe IP, et al. A critical role for *Vibrio parahaemolyticus* LPS to mediate evasion of host immune response during infection[J]. Proc Natl Acad Sci USA, 2025, 122(33): e2426547122. doi: 10.1073/pnas.2426547122.

[18] Hong M, Li Z, Liu H, et al. *Fusobacterium nucleatum* aggravates rheumatoid arthritis through FadA-containing outer membrane vesicles[J]. Cell Host Microbe, 2023, 31(5): 798-810. e7. doi: 10.1016/j.chom.2023.03.018.

[19] Oh SY, Kim DY, Lee KY, et al. *Streptococcus mutans*-derived extracellular vesicles promote skin wound healing *via* tRNA cargo[J]. J Nanobiotechnology, 2025, 23(1): 322. doi: 10.1186/s12951-025-03410-1.

[20] Xie Z, Wang X, Huang Y, et al. *Pseudomonas aeruginosa* outer membrane vesicle-packed sRNAs can enter host cells and regulate innate immune responses[J]. Microb Pathog, 2024, 188: 106562. doi: 10.1016/j.micpath.2024.106562.

[21] Sheikh A, Scano C, Xu J, et al. Outer membrane vesicles from *Bacteroides fragilis* contain coding and non-coding small RNA species that modulate inflammatory signalling in intestinal epithelial cells[J]. J Extracell Biol, 2025, 4(10): e70086. doi: 10.1002/jex2.70086.

[22] Kumar MA, Baba SK, Sadida HQ, et al. Extracellular vesicles as tools and targets in therapy for diseases[J]. Signal Transduct Target Ther, 2024, 9(1): 27. doi: 10.1038/s41392-024-01735-1.

[23] Preet R, Islam MA, Shim J, et al. Gut commensal *Bifidobacterium*-derived extracellular vesicles modulate the therapeutic effects of anti-PD-1 in lung cancer[J]. Nat Commun, 2025, 16(1): 3500. doi: 10.1038/s41467-025-58553-4.

[24] Hezaveh K, Shinde RS, Klötgen A, et al. Tryptophan-derived microbial metabolites activate the aryl hydrocarbon receptor in tumor-associated macrophages to suppress anti-tumor immunity[J]. Immunity, 2022, 55(2): 324-340. e8. doi: 10.1016/j.immuni.2022.01.006.

[25] Wang X, Lin S, Wang L, et al. Versatility of bacterial outer membrane vesicles in regulating intestinal homeostasis[J]. Sci Adv, 2023, 9(11): eade5079. doi: 10.1126/sciadv.ade5079.

[26] Xie J, Cools L, Van Imschoot G, et al. *Helicobacter pylori*-derived outer membrane vesicles contribute to Alzheimer's disease pathogenesis *via* C3-C3aR signalling[J]. J Extracell Vesicles, 2023, 12(2): 12306. doi: 10.1002/jev2.12306.

[27] Iwabuchi Y, Nakamura T, Kusumoto Y, et al. Effects of pH on the

properties of membrane vesicles including glucosyltransferase in *Streptococcus mutans*[J]. Microorganisms, 2021, 9(11): 2308. doi: 10.3390/microorganisms9112308.

[28] Wen ZT, Jorgensen AN, Huang X, et al. Multiple factors are involved in regulation of extracellular membrane vesicle biogenesis in *Streptococcus mutans*[J]. Mol Oral Microbiol, 2021, 36(1): 12-24. doi: 10.1111/omi.12318.

[29] Nagasawa R, Yamamoto T, Utada AS, et al. Competence-stimulating-peptide-dependent localized cell death and extracellular DNA production in *Streptococcus mutans* biofilms[J]. Appl Environ Microbiol, 2020, 86(23): e02080-20. doi: 10.1128/AEM.02080-20.

[30] Cui G, Li P, Wu R, et al. *Streptococcus mutans* membrane vesicles inhibit the biofilm formation of *Streptococcus gordonii* and *Streptococcus sanguinis*[J]. AMB Express, 2022, 12(1): 154. doi: 10.1186/s13568-022-01499-3.

[31] Wu R, Cui G, Cao Y, et al. *Streptococcus mutans* membrane vesicles enhance *Candida albicans* pathogenicity and carbohydrate metabolism[J]. Front Cell Infect Microbiol, 2022, 12: 940602. doi: 10.3389/fcimb.2022.940602.

[32] Zhang Y, Gu Z, Li Z, et al. *Streptococcus mutans* regulates ubiquitin modification of *Candida albicans* in the bacterial-fungal interaction[J]. PLoS Pathog, 2025, 21(2): e1012887. doi: 10.1371/journal.ppat.1012887.

[33] Liao S, Klein MI, Heim KP, et al. *Streptococcus mutans* extracellular DNA is upregulated during growth in biofilms, actively released *via* membrane vesicles, and influenced by components of the protein secretion machinery[J]. J Bacteriol, 2014, 196(13): 2355-2366. doi: 10.1128/JB.01493-14.

[34] Song G, Li M, Zhou B, et al. *Streptococcus mutans* outer membrane vesicles affect inflammasome activation and the glycolysis of macrophages[J]. Microb Pathog, 2024, 196: 106994. doi: 10.1016/j.micpath.2024.106994.

[35] Johnston EL, Guy-Von Stieglitz S, Zavan L, et al. The effect of altered pH growth conditions on the production, composition, and proteomes of *Helicobacter pylori* outer membrane vesicles[J]. Proteomics, 2024, 24(11): e2300269. doi: 10.1002/pmic.202300269.

[36] Nonaka S, Kadowaki T, Nakanishi H. Secreted gingipains from *Porphyromonas gingivalis* increase permeability in human cerebral microvascular endothelial cells through intracellular degradation of tight junction proteins[J]. Neurochem Int, 2022, 154: 105282. doi: 10.1016/j.neuint.2022.105282.

[37] Huang X, Xie M, Wang Y, et al. *Porphyromonas gingivalis* aggravates atherosclerotic plaque instability by promoting lipid-laden macrophage necroptosis[J]. Signal Transduct Target Ther, 2025, 10(1): 171. doi: 10.1038/s41392-025-02251-6.

[38] Shiheido-Watanabe Y, Maejima Y, Nakagama S, et al. *Porphyromonas gingivalis*, a periodontal pathogen, impairs post-infarcted myocardium by inhibiting autophagosome-lysosome fusion[J]. Int J Oral Sci, 2023, 15(1): 42. doi: 10.1038/s41368-023-00251-2.

[39] Alaei SR, King AJ, Banani K, et al. Lipid a remodeling modulates outer membrane vesicle biogenesis by *Porphyromonas gingivalis*[J]. J Bacteriol, 2025, 207(1): e0033624. doi: 10.1128/jb.00336-24.

[40] Domae E, Mori T, Hanaoka M, et al. Recognition of *Porphyromonas gingivalis* lipopolysaccharide by human caspase-4 depends on lipopolysaccharide purity and guanylate-binding protein 1[J]. J Oral Microbiol, 2025, 17(1): 2589652. doi: 10.1080/20002297.2025.2589652.

[41] Veloso P, Fernández A, Astorga J, et al. Lipopolysaccharide from *Porphyromonas gingivalis*, but not from *Porphyromonas endodontalis*, induces macrophage M1 profile[J]. Int J Mol Sci, 2022, 23(17): 10011. doi: 10.3390/ijms231710011.

[42] Angabo S, Pandi K, David K, et al. CD47 and thrombospondin-1 contribute to immune evasion by *Porphyromonas gingivalis*[J]. Proc Natl Acad Sci USA, 2024, 121(47): e2405534121. doi: 10.1073/pnas.2405534121.

[43] Pandi K, Angabo S, Gnanasekaran J, et al. *Porphyromonas gingivalis* induction of TLR2 association with vinculin enables PI3K activation and immune evasion[J]. PLoS Pathog, 2023, 19(4): e1011284. doi: 10.1371/journal.ppat.1011284.

[44] Yan Y, Wang H, Deng H, et al. *Porphyromonas gingivalis* OMVs inhibit osteogenic differentiation of BMSCs *via* SAA3/TLR4/MyD88/NF-κB axis[J]. J Oral Microbiol, 2025, 17(1): 2540823. doi: 10.1080/20002297.2025.2540823.

[45] Qiu Q, Yan X, Zhang Z, et al. *Porphyromonas gingivalis* extracellular vesicles exacerbated osteoporosis by disrupting osteoblast mitochondrial dynamics and inhibiting Cpt2-regulated fatty acid oxidation[J]. J Nanobiotechnology, 2025, 23(1): 635. doi: 10.1186/s12951-025-03717-z.

[46] Luo X, Wang Y, Ning T, et al. Outer membrane vesicles of *Porphyromonas gingivalis* impede bone regeneration by inducing ferroptosis *via* the Hippo-YAP signaling pathway[J]. J Nanobiotechnology, 2025, 23(1): 358. doi: 10.1186/s12951-025-03457-0.

[47] Muchova M, Balacco DL, Grant MM, et al. *Fusobacterium nucleatum* subspecies differ in biofilm forming ability *in vitro*[J]. Front Oral Health, 2022, 3: 853618. doi: 10.3389/froh.2022.853618.

[48] Liu L, Liang L, Yang C, et al. Extracellular vesicles of *Fusobacterium nucleatum* compromise intestinal barrier through targeting RIPK1-mediated cell death pathway[J]. Gut Microbes, 2021, 13(1): 1-20. doi: 10.1080/19490976.2021.1902718.

[49] Chen G, Sun Q, Cai Q, et al. Outer membrane vesicles from *Fusobacterium nucleatum* switch M0-like macrophages toward the M1 phenotype to destroy periodontal tissues in mice[J]. Front Microbiol, 2022, 13: 815638. doi: 10.3389/fmicb.2022.815638.

[50] Engevik MA, Danhof HA, Ruan W, et al. *Fusobacterium nucleatum* secretes outer membrane vesicles and promotes intestinal inflammation[J]. mBio, 2021, 12(2): e02706-20. doi: 10.1128/mBio.02706-20.

[51] Kang W, Ji X, Zhang X, et al. Persistent exposure to *Fusobacterium nucleatum* triggers chemokine/cytokine release and inhibits the proliferation and osteogenic differentiation capabilities of human gingiva-derived mesenchymal stem cells[J]. Front Cell Infect Microbiol, 2019, 9: 429. doi: 10.3389/fcimb.2019.00429.

[52] Kim HY, Song MK, Lim Y, et al. Effects of extracellular vesicles derived from oral bacteria on osteoclast differentiation and activa-

tion[J]. Sci Rep, 2022, 12(1): 14239. doi: 10.1038/s41598-022-18412-4.

[53] Qi M, Ding Q, Shi Y, et al. NIR-activated nanodisguisers for targeted bactericidal action and enhanced electron transfer in periodontitis treatment[J]. Biomaterials, 2026, 324: 123487. doi: 10.1016/j.biomaterials.2025.123487.

[54] Kieselbach T, Zijnge V, Granström E, et al. Proteomics of *Aggregatibacter actinomycetemcomitans* outer membrane vesicles[J]. PLoS One, 2015, 10(9): e0138591. doi: 10.1371/journal.pone.0138591.

[55] Nice JB, Collins SM, Agro SMJ, et al. Heterogeneity of size and toxin distribution in *Aggregatibacter actinomycetemcomitans* outer membrane vesicles[J]. Toxins (Basel), 2024, 16(3): 138. doi: 10.3390/toxins16030138.

[56] Cecil JD, O'Brien-Simpson NM, Lenzo JC, et al. Differential responses of pattern recognition receptors to outer membrane vesicles of three periodontal pathogens[J]. PLoS One, 2016, 11(4): e0151967. doi: 10.1371/journal.pone.0151967.

[57] Cecil JD, O'Brien-Simpson NM, Lenzo JC, et al. Outer membrane vesicles prime and activate macrophage inflammasomes and cytokine secretion *in vitro* and *in vivo*[J]. Front Immunol, 2017, 8: 1017. doi: 10.3389/fimmu.2017.01017.

[58] Martin-Gallausiaux C, Malabirade A, Habier J, et al. *Fusobacterium nucleatum* extracellular vesicles modulate gut epithelial cell innate immunity *via* FomA and TLR2[J]. Front Immunol, 2020, 11: 583644. doi: 10.3389/fimmu.2020.583644.

[59] Chen G, Gao C, Jiang S, et al. *Fusobacterium nucleatum* outer membrane vesicles activate autophagy to promote oral cancer metastasis[J]. J Adv Res, 2024, 56: 167-179. doi: 10.1016/j.jare.2023.04.002.

[60] Lamprinaki D, Garcia-Vello P, Marchetti R, et al. Siglec-7 mediates immunomodulation by colorectal cancer-associated *Fusobacterium nucleatum* ssp. animalis[J]. Front Immunol, 2021, 12: 744184. doi: 10.3389/fimmu.2021.744184.

[61] 邹捷康, 曹宇蒙, 田义, 等. 牙龈卟啉单胞菌外膜囊泡携带脂多糖激活Toll样受体2促进破骨细胞分化的研究[J]. 中华口腔医学杂志, 2024, 59(3): 237-246. doi: 10.3760/cma. j. cn112144-20231026-00222.
Zou JK, Cao YM, Tian Y, et al. *Porphyromonas gingivalis* outer membrane vesicles activate Toll-like receptor 2 to promote osteoclast differentiation by carrying lipopolysaccharide[J]. Chin J Stomatol, 2024, 59(3): 237-246. doi: 10.3760/cma. j. cn112144-20231026-00222.

[62] Ma RY, Deng ZL, Du QY, et al. *Enterococcus faecalis* extracellular vesicles promote apical periodontitis[J]. J Dent Res, 2024, 103(6): 672-682. doi: 10.1177/00220345241230867.

[63] Yuan Z, Huang W, Chan P, et al. Membrane vesicles of *Enterococcus faecalis*: *in vitro* composition analysis and macrophage inflammatory response under different pH conditions[J]. Microorganisms, 2025, 13(6): 1344. doi: 10.3390/microorganisms13061344.

[64] Fan R, Zhou Y, Chen X, et al. *Porphyromonas gingivalis* outer membrane vesicles promote apoptosis *via* msRNA-regulated DNA methylation in periodontitis[J]. Microbiol Spectr, 2023, 11(1): e0328822. doi: 10.1128/spectrum.03288-22.

[65] Huang B, Liu C, Yang J, et al. Saliva biofilm-derived outer membrane vesicles regulate biofilm formation and immune response of oral epithelial cells on titanium surfaces[J]. Clin Oral Investig, 2024, 28(1): 75. doi: 10.1007/s00784-023-05454-9.

[66] Furuta N, Takeuchi H, Amano A. Entry of *Porphyromonas gingivalis* outer membrane vesicles into epithelial cells causes cellular functional impairment[J]. Infect Immun, 2009, 77(11): 4761-4770. doi: 10.1128/IAI.00841-09.

[67] Grenier D. *Porphyromonas gingivalis* outer membrane vesicles mediate coaggregation and piggybacking of *Treponema denticola* and *Lachnoanaerobaculum saburreum*[J]. Int J Dent, 2013, 2013: 305476. doi: 10.1155/2013/305476.

[68] Guo J, Lin K, Wang S, et al. Effects and mechanisms of *Porphyromonas gingivalis* outer membrane vesicles induced cardiovascular injury[J]. BMC Oral Health, 2024, 24(1): 112. doi: 10.1186/s12903-024-03886-7.

[69] Gong T, Chen Q, Mao H, et al. Outer membrane vesicles of *Porphyromonas gingivalis* trigger NLRP3 inflammasome and induce neuroinflammation, tau phosphorylation, and memory dysfunction in mice[J]. Front Cell Infect Microbiol, 2022, 12: 925435. doi: 10.3389/fcimb.2022.925435.

[70] Ma X, Shin YJ, Yoo JW, et al. Extracellular vesicles derived from *Porphyromonas gingivalis* induce trigeminal nerve-mediated cognitive impairment[J]. J Adv Res, 2023, 54: 293-303. doi: 10.1016/j.jare.2023.02.006.

[71] Zhao Q, Maynard CL. Mucus, commensals, and the immune system [J]. Gut Microbes, 2022, 14(1): 2041342. doi: 10.1080/19490976.2022.2041342.

[72] Chasov V, Gilyazova E, Ganeeva I, et al. Gut microbiota modulation: a novel strategy for rheumatoid arthritis therapy[J]. Biomolecules, 2024, 14(12): 1653. doi: 10.3390/biom14121653.

[73] Huang S, Cao G, Dai D, et al. *Porphyromonas gingivalis* outer membrane vesicles exacerbate retinal microvascular endothelial cell dysfunction in diabetic retinopathy[J]. Front Microbiol, 2023, 14: 1167160. doi: 10.3389/fmicb.2023.1167160.

[74] Seyama M, Yoshida K, Yoshida K, et al. Outer membrane vesicles of *Porphyromonas gingivalis* attenuate insulin sensitivity by delivering gingipains to the liver[J]. Biochim Biophys Acta Mol Basis Dis, 2020, 1866(6): 165731. doi: 10.1016/j.bbadis.2020.165731.

[75] Wei S, Zhang J, Wu X, et al. *Fusobacterium nucleatum* extracellular vesicles promote experimental colitis by modulating autophagy *via* the miR-574-5p/CARD3 axis[J]. Inflamm Bowel Dis, 2023, 29 (1): 9-26. doi: 10.1093/ibd/izac177.

[76] Wang J, Liu C, Cutler J, et al. Microbial- and host immune cell-derived extracellular vesicles in the pathogenesis and therapy of periodontitis: a narrative review[J]. J Periodontal Res, 2024, 59(6): 1115-1129. doi: 10.1111/jre.13283.

[77] Byun JS, Lee HY, Tian J, et al. Effect of salivary exosomal miR-25-3p on periodontitis with insulin resistance[J]. Front Immunol, 2022, 12: 775046. doi: 10.3389/fimmu.2021.775046.

[78] Ni J, Zhang Q, Lei F. Non-invasive diagnostic potential of salivary miR-25-3p for periodontal disease and osteoporosis among a co-

hort of elderly patients with type 2 diabetes mellitus[J]. BMC Oral Health, 2023, 23(1): 318. doi: 10.1186/s12903-023-02992-2.

[79] Farrugia C, Stafford GP, Murdoch C. *Porphyromonas gingivalis* outer membrane vesicles increase vascular permeability[J]. J Dent Res, 2020, 99(13): 1494-1501. doi: 10.1177/0022034520943187.

[80] Tang Y, Zhao X, Ding Z, et al. Novel hybrid peptide DEFB126 (1-39)-TP5 inhibits LPS-induced inflammatory responses and oxidative stress by neutralizing LPS and blocking the TLR4/MD2-NFκB signaling axis[J]. Antioxidants (Basel), 2025, 14(9): 1117. doi: 10.3390/antiox14091117.

[81] Wang Y, Guo W, Zhang K, et al. Biomimetic electrodynamic metal-organic framework nanosponges for augmented treatment of biofilm infections[J]. Adv Sci (Weinh), 2024, 11(46): e2408442. doi: 10.1002/advs.202408442.

[82] Kim SH, Kim KS, Lee SR, et al. Structural modifications of outer membrane vesicles to refine them as vaccine delivery vehicles[J]. Biochim Biophys Acta, 2009, 1788(10): 2150-2159. doi: 10.1016/j.bbamem.2009.08.001.

[83] Shen X, Wang S, Qiu K, et al. Engineered low-endotoxin bacterial biomimetic vesicles for enhanced oral dual-antigen subunit vaccine delivery[J]. J Extracell Vesicles, 2025, 14(12): e70207. doi: 10.1002/jev2.70207.

[84] Xiang Y, Liu Q, Liu K, et al. An exosome-based nanoplatform for siRNA delivery combined with starvation therapy promotes tumor cell death through autophagy, overcoming refractory KRAS-mutated tumors and restoring cetuximab chemosensitivity[J]. Mater Today Bio, 2025, 32: 101732. doi: 10.1016/j.mtbio.2025.101732.

[85] Zhou H, Qi YX, Zhu CH, et al. Mesenchymal stem cell-derived extracellular vesicles for treatment of bone loss within periodontitis in pre-clinical animal models: a meta-analysis[J]. BMC Oral Health, 2023, 23(1): 701. doi: 10.1186/s12903-023-03398-w.

[86] Fang A, Wang Y, Guan N, et al. Porous microneedle patch with sustained delivery of extracellular vesicles mitigates severe spinal cord injury[J]. Nat Commun, 2023, 14(1): 4011. doi: 10.1038/s41467-023-39745-2.

[87] Zhou L, Liu Q, Fang Z, et al. Targeted antimicrobial self-assembly peptide hydrogel with *in situ* bio-mimic remineralization for caries management[J]. Bioact Mater, 2024, 44: 428-446. doi: 10.1016/j.bioactmat.2024.10.022.

[88] Chen Y, Lin S, Huang X, et al. From biofilm control to biomimetic remineralization: hydrogels in prevention and treatment of dental caries[J]. Front Cell Infect Microbiol, 2025, 15: 1663563. doi: 10.3389/fcimb.2025.1663563.

[89] Bracht JWP, Los M, van der Pol E, et al. Choice of size-exclusion chromatography column affects recovery, purity, and miRNA cargo analysis of extracellular vesicles from human plasma[J]. Extracell Vesicles Circ Nucl Acids, 2024, 5(3): 497-508. doi: 10.20517/evcna.2024.34.

[90] Jia Y, Yu L, Ma T, et al. Small extracellular vesicles isolation and separation: current techniques, pending questions and clinical applications[J]. Theranostics, 2022, 12(15): 6548-6575. doi: 10.7150/thno.74305.

[91] Brennan K, Martin K, FitzGerald SP, et al. A comparison of methods for the isolation and separation of extracellular vesicles from protein and lipid particles in human serum[J]. Sci Rep, 2020, 10(1): 1039. doi: 10.1038/s41598-020-57497-7.

[92] Iwai K, Minamisawa T, Suga K, et al. Isolation of human salivary extracellular vesicles by iodixanol density gradient ultracentrifugation and their characterizations[J]. J Extracell Vesicles, 2016, 5: 30829. doi: 10.3402/jev.v5.30829.

[93] Akbar A, Malekian F, Baghban N, et al. Methodologies to isolate and purify clinical grade extracellular vesicles for medical applications[J]. Cells, 2022, 11(2): 186. doi: 10.3390/cells11020186.

[94] 孙岩, 程磊, 彭显. 唾液外泌体与口腔疾病相关研究进展[J]. 口腔疾病防治, 2022, 30(4): 300-304. doi: 10.12016/j.issn.2096-1456.2022.04.012.
Sun Y, Cheng L, Peng X. Research progress on salivary exosomes and oral diseases[J]. J Prev Treat Stomatol Dis, 2022, 30(4): 300-304. doi: 10.12016/j.issn.2096-1456.2022.04.012.

[95] Greening DW, Rai A, Simpson RJ. Extracellular vesicles-an omics view[J]. Proteomics, 2024, 24(11): e2400128. doi: 10.1002/pmic.202400128.

[96] Rai A, Huynh K, Cross J, et al. Multi-omics identify hallmark protein and lipid features of small extracellular vesicles circulating in human plasma[J]. Nat Cell Biol, 2025, 27(12): 2167-2185. doi: 10.1038/s41556-025-01795-7.

[97] Qiu L, Liu X, Zhu L, et al. Current advances in technologies for single extracellular vesicle analysis and its clinical applications in cancer diagnosis[J]. Biosensors (Basel), 2023, 13(1): 129. doi: 10.3390/bios13010129.

[98] Wu J, Dou Q, Mao M, et al. Single extracellular vesicle imaging *via* rolling circle amplification-expansion microscopy[J]. Nat Commun, 2025, 16(1): 7498. doi: 10.1038/s41467-025-62613-0.

[99] Zhang YY, Li YL, Song QX, et al. Engineered RVG-exosomes-mediated delivery of siRNAs targeting NMDAR alleviates orofacial neuropathic pain by suppressing central sensitivity[J]. J Pain, 2025, 33: 105457. doi: 10.1016/j.jpain.2025.105457.

[100] Lin X, Lin L, Wu J, et al. A targeted siRNA-loaded PDL1-exosome and functional evaluation against lung cancer[J]. Thorac Cancer, 2022, 13(11): 1691-1702. doi: 10.1111/1759-7714.14445.

[101] Chen H, Wang L, Zeng X, et al. Exosomes, a new star for targeted delivery[J]. Front Cell Dev Biol, 2021, 9: 751079. doi: 10.3389/fcell.2021.751079.

（编辑　周春华）

官网