

· 口腔感染微生态专栏·综述·

益生菌水凝胶在龋病防治中的研究进展

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【摘要】 龋病作为全球高发的慢性感染性疾病,其传统预防药物(如抗菌剂和氟化物)存在诱导耐药性与破坏口腔微生态平衡等局限。益生菌“以菌制菌”的微生态调控策略成为防治新思路,但临床现有益生菌产品普遍存在口腔滞留时间短、易被唾液冲刷和难以在牙面有效定植等问题。而水凝胶作为新型递送体系,能高效包载益生菌并实现病灶靶向定植,显著延长作用时间,通过竞争排斥致龋菌、调节pH值、分泌抑菌物及调节免疫等途径发挥作用。本文综述了益生菌防龋水凝胶的研究进展,重点阐述防龋原理、菌株筛选原则、水凝胶设计机制及降解动力学对递送与治疗的调控作用,旨在为龋病的微生态防治与临床转化提供理论参考。

【关键词】 益生菌; 水凝胶; 龋病防治; 口腔微生态

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Research progress of probiotic hydrogels in the prevention and treatment of dental caries

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【Abstract】 Dental caries is a highly prevalent chronic infectious disease worldwide. However, traditional preventive agents, such as antimicrobials and fluorides, face limitations including the induction of bacterial resistance and disruption of oral microecological balance. Emerging as a novel strategy, microecological regulation using probiotics to "combat bacteria with bacteria" offers a promising alternative for caries prevention. Nevertheless, current clinical probiotic products

generally suffer from short retention times in the oral cavity, susceptibility to saliva rinsing, and difficulty in achieving effective colonization on dental surfaces. As an innovative delivery system, hydrogels can efficiently encapsulate probiotics, achieve lesion-targeted colonization, and significantly prolong retention time. These hydrogel systems exert anti-caries effects through competitive exclusion of cariogenic bacteria, pH regulation, secretion of antimicrobial substances, and immune modulation. This article reviews recent research progress on probiotic-loaded anti-caries hydrogels, with a particular focus on the anti-caries mechanisms, principles of strain selection, hydrogel design mechanisms, and the regulatory roles of degradation kinetics in probiotic delivery and therapy. Overall, this review aims to provide a theoretical reference for the microecological prevention and clinical translation of dental caries.

【Key words】 Probiotics; Hydrogels; Caries prevention and treatment; Oral microecology

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龋病是全球高发的慢性口腔感染性疾病,构成严重公共卫生负担^[1]。其核心机制是口腔微生态失衡,致龋菌如变异链球菌(*Streptococcus mutans*, *S. mutans*)通过构建生物膜和产酸导致牙体脱矿^[2]。传统氟化物和抗菌剂虽可延缓病程,但在抑制产酸、阻断生物膜及恢复微生态方面存在局限性^[3]。因此,如何精准靶向致病环节并协同重建微生态平衡已成为研究热点。近年来,益生菌疗法作为一种“以菌制菌”的微生态制衡策略,在龋病防治领域展现出巨大的应用潜力^[4]。然而,传统临床制剂中的益生菌常受限于口腔内滞留时间短、唾液持续冲刷导致的局部有效浓度不足,以及难以精准靶向窝沟与邻面等龋病好发解剖位点等瓶颈^[5]。水凝胶递送系统凭借其优异的生物黏附性、药物缓释动力学特性及良好的生物相容性,可有效维持益生菌的生物活性,延长其在口腔微环境中的滞留窗口期,并实现特定定位点的精准递送,从而显著增强其抗龋效能。智能水凝胶因生物相容性好、性能可调且能负载益生菌,可有效抑制致龋菌、调节口腔微环

境^[6]。本文综述了益生菌水凝胶在龋病防治中的最新进展,重点分析其设计策略与防龋机制,为新型生物材料研发与临床转化提供参考。

一、益生菌防龋的理论基础

1. 口腔微生态与龋病发生的关系:口腔微生态是由细菌、真菌、病毒等构成的复杂共生系统,其中细菌为优势类群,广泛定植于牙面、牙龈和舌背等部位,形成动态平衡的群落。在健康状态下,口腔微生态具有物种多样性高、优势菌群稳定、代谢平衡等特点,有益菌群与有害菌群相互制约,共同维持微环境稳态^[7-8]。基于生态菌斑假说,龋病本质是微生态失衡的结果。当饮食、口腔卫生、免疫力等因素改变时,有害菌群(如 *S. mutans*)异常增殖,有益菌群减少,多样性下降,致龋菌通过形成生物膜并产酸,使局部 pH 值持续低于 5.5,打破牙体脱矿-再矿化平衡,导致龋损发生^[9]。当前龋病预防仍以机械性清除菌斑为主。传统防龋辅助制剂中,抗菌剂(如氯己定)虽能抑制致龋菌,但选择性差,易扰乱口腔微生态平衡并诱导耐药^[10];氟化物主要通过促进再矿化发挥作用,其直接抑菌活性微弱,难以从根本上纠正微生态失衡,且

存在诱发氟斑牙等毒副作用风险^[11]。因此,靶向调控口腔菌群的益生菌制剂凭借其生态防控优势,已成为当前研究热点^[12]。

2. 益生菌防龋的作用原理:益生菌主要通过竞争性抑制、微生态重构及免疫调控三重机制发挥防龋作用。首先,益生菌凭借表面的黏附因子,与 *S. mutans* 等致龋菌竞争牙面及牙菌斑内的定植位点与营养资源。这种竞争性排斥可阻断致龋菌早期黏附及生物膜形成,从早期阶段干预龋病的发生发展^[13]。其次,定植后的益生菌通过补充有益菌群、优化菌群结构并提升微生物多样性,协同重建口腔微生态稳态,进而消除致龋微环境^[12]。此外,益生菌可激活口腔黏膜免疫系统,增强屏障功能与免疫应答以提升宿主抵抗力,同时通过抑制过度炎症反应保护黏膜组织,实现间接防龋效应^[14]。

3. 防龋益生菌的常见种类:防龋益生菌的筛选需满足口腔定植能力强、抗菌活性显著和安全性高的要求,目前研究较多且效果明确的种类见表 1,其中乳杆菌属和双歧杆菌属是研究最广泛的两大类群。

4. 防龋益生菌的目标菌群筛选标准:筛选高效防龋益生

表 1 主要防龋益生菌种属及其防龋机制汇总

菌属	代表菌株	拉丁学名(缩写)	核心防龋作用与特点	临床 RCT 证据
乳杆菌属 (核心类群)	罗伊氏乳杆菌	<i>Lactobacillus reuteri</i> (<i>L. reuteri</i>)	有效抑制 <i>S. mutans</i> 黏附与定植,调节口腔 pH 值,防龋领域研究与应用最广泛 ^[15] ,现有证据支持其防龋效果较为明确。	一项针对幼儿的 12 个月 RCT 显示,含 DSM 17938 的滴剂未能降低新发龋齿发生率(两组均为 67%)。另有 RCT 显示可减少 <i>S. mutans</i> ,但对已形成的龋病无逆转效果 ^[16] 。
	植物乳杆菌	<i>Lactiplantibacillus plantarum</i> (<i>L. plantarum</i>)	抑菌活性、口腔定植能力强,安全性高,对 <i>S. mutans</i> 生物膜具有抑制效果 ^[17] ,应用潜力大。	目前仅有体外生物膜模型研究证实其抑菌效果。缺乏以 <i>S. mutans</i> 计数或龋齿发生率为终点的人体 RCT。
	干酪乳杆菌	<i>Lactobacillus casei</i> (<i>L. casei</i>)	核心防龋益生菌类群成员,参与口腔微生态调节 ^[8] ,辅助抑制致龋菌。	有一项 RCT 显示,含 <i>L. casei</i> 的酸奶可暂时降低唾液中 <i>S. mutans</i> 水平,但效果在停止摄入后 2 周即消失。未评估龋齿终点 ^[18] 。
	嗜酸乳杆菌	<i>Lactobacillus acidophilus</i> (<i>L. acidophilus</i>)	乳杆菌属核心防龋菌株,助力维持口腔微生态平衡 ^[19] 。	绝大多数研究为含多种菌株的复合益生菌产品(常与 <i>L. rhamnosus</i> 、双歧杆菌联用),无法单独归因于 <i>L. acidophilus</i> 。单独使用的 RCT 非常稀缺。
双歧杆菌属	婴儿双歧杆菌	<i>Bifidobacterium infantis</i> (<i>B. infantis</i>)	通过竞争性排斥抑制致龋菌 ^[20] ,调节口腔微生态与宿主免疫,安全性高,适合防龋产品开发。	目前所有 RCT 均针对肠道健康或过敏性疾病。在口腔防龋领域,没有任何以口腔菌群或龋齿为终点的人体研究。
	长双歧杆菌	<i>Bifidobacterium longum</i> (<i>B. longum</i>)	同上,竞争性抑制致龋菌生长,调节免疫与微生态 ^[21] ,辅助防龋。	与 <i>B. infantis</i> 类似,现有 RCT 集中于肠道和免疫调节。缺乏口腔防龋的人体研究证据。
链球菌属 (口腔固有有益菌)	唾液链球菌	<i>Streptococcus salivarius</i> (<i>S. salivarius</i>)	口腔天然有益菌,分泌抗菌物质抑制 <i>S. mutans</i> ,维持微生态稳态 ^[22] ,定植与相容性好。	一项 RCT 显示 M18+K12 组合反而使 <i>S. mutans</i> 显著增加(750→1 700 CFU/mL)。另有两项 RCT 分别显示 K12 或 M18 单用可减少 <i>S. mutans</i> 。提示特定组合可能有害 ^[23] 。
	血链球菌	<i>Streptococcus sanguinis</i> (<i>S. sanguinis</i>)	口腔固有有益菌,抑制致龋菌生长 ^[24] ,参与维持口腔微生态平衡。	所有研究均为观察性横断面研究,发现龋活跃者体内 <i>S. sanguinis</i> 丰度较低。没有任何以口服该菌株作为干预手段的 RCT。
其他潜在防龋益生菌	鼠李糖乳杆菌	<i>Lactocaseibacillus rhamnosus</i> (<i>L. rhamnosus</i>)	可减少致龋菌数量、调节唾液 pH、降低龋病活性 ^[25] ,为重要候选菌株。	一项针对幼儿的 6 个月 RCT 显示, <i>L. rhamnosus</i> SD11 可显著降低龋齿进展率(3.48% vs. 4.55%),同时减少 <i>S. mutans</i> 。另有短期 RCT 证实可抑制致龋菌 ^[26] 。

注:*S. mutans* 为变异链球菌;RCT 为随机对照试验。

菌需遵循特异性、安全性、有效性和定植性的核心原则,并从以下6个维度综合评价。

(1)定植能力与环境耐受性:菌株须具备强的口腔黏附力,能抵抗唾液剪切力、溶菌酶及pH(5.0~7.0)波动,可通过表面疏水性、电荷性质、胞外多糖产量及自聚能力等指标评估其定植潜力^[27]。

(2)抗菌活性与代谢特征:菌株应对 *S.mutans* 等主导致龋菌表现出显著抑制效果[抑菌圈直径 ≥ 10 mm,且最低抑菌浓度(minimum inhibitory concentration, MIC)值较低],同时优先选择产生非有机酸类抑菌代谢产物的菌株,以降低口腔酸性负荷^[28]。

(3)生物安全性:候选菌株必须无致病性、无溶血活性且不产生毒素,对抗生素无或低耐药性,经产酸性评价确保其对牙体硬组织无腐蚀性,并通过抗生素敏感性试验^[29]。

(4)微生态相容性:菌株应与口腔固有有益菌群协同共生,在不抑制天然益生菌增殖的前提下,维持口腔微生态平衡,且与宿主黏膜无免疫排斥^[30]。

(5)环境稳定性与产业适配性:菌株需在口腔复杂环境及制剂加工、储存过程中维持高活菌率,适配规模化生产需求。

(6)多功能协同效应:除核心防龋功能外,理想菌株还应兼具免疫调节、促进牙体再矿化及增强唾液缓冲等辅助功效,为龋病综合防治提供多靶点支撑^[30]。

二、防龋益生菌水凝胶的设计与构建

1. 水凝胶作为益生菌载体的优势与要求:传统益生菌递送至口腔的剂型(如漱口水、片剂或咀嚼胶),普遍面临滞留时间短、易被唾液冲刷或吞咽,以及菌体在加工与储存过程中活力难以维持的挑战^[31]。相比之下,水凝胶载体凭借其独特的物理化学性质,在防龋领域展现出显著的优势。首先,水凝胶可通过调控含水率、渗透压及pH值^[32],具备抵御制备及存储过程中理化胁迫的稳态保护能力,实现益生菌的高包封率与活力保持^[33-34]。其次,水凝胶可实现益生菌在牙菌斑生物膜靶区的“按需释放”与动力学可控递送,可显著缓解因瞬时突释(burst release)引发的药效下降问题,例如酶响应型水凝胶可利用菌斑代谢酶介导的酶响应机制实现靶向释药物^[35]。再者,水凝胶可作为共递送平台,同时包载益生菌和其他活性成分(如氟化物、钙锶硅酸盐),发挥协同防龋效应。此外,水凝胶基质应具备良好的生物安全性与黏膜组织相容性,符合口腔医疗器械或食品级的安全评价规范,如天然多糖及半合成聚合物已成为理想载体材料^[36]。最后,通过引入阳离子聚合物介导的静电吸附作用,水凝胶可显著延长在口腔黏膜靶区的滞留时间;或通过构建黏膜黏附型水凝胶,制备贴合牙面的贴片或膜剂,进一步增强定位滞留效果。

2. 常用水凝胶基质材料:包括天然高分子材料、合成与半合成高分子材料。

(1)天然高分子材料:天然高分子因其卓越的生物安全性与可修饰性,成为构建载体的主流基质。壳聚糖(chitosan, CS)质子化后带正电荷,依靠静电相互作用结合黏

膜蛋白负电基团,实现黏膜黏附效果^[37];海藻酸钠则利用二价阳离子(如 Ca^{2+})介导的快速交联^[38-39],在温和条件下最大限度保留益生菌活性。此外,明胶可利用其精氨酸-甘氨酸-天冬氨酸(arginine-glycine-aspartic acid, RGD)序列促进细胞黏附^[40]。尽管优势显著,但单一组分常面临力学模量低、降解动力学难控等瓶颈。目前的主流改性逻辑是通过物理/化学杂化(如季铵化CS)^[41]或引入动态共价键与纳米填料(如Zr-MOC)^[42],在保留生物友好性的核心优势下显著提升结构的鲁棒性。

(2)合成与半合成高分子材料:此类材料为水凝胶提供了高度可编程的工程化平台,通过调控分子量及交联密度实现理化性质的按需定制。其中,泊洛沙姆(如Pluronic F127)展现出显著的热致相变行为,其低温溶胶-体温凝胶的特性极大地适配了口腔微创递送场景^[43-44];聚乙二醇(polyethylene glycol, PEG)及其衍生物的生物相容性好,结构可控,可通过光交联等方式形成网络^[45],常与天然材料复合以提高机械性能^[46-47]。由于纯合成材料在生物相容性及代谢归趋方面存在瓶颈,当前的研究逻辑趋向于构建天然-合成杂化体系,通过整合生物活性基团实现理化性能与生物安全性的协同优化。

3. 水凝胶的制备方法与益生菌封装技术:益生菌防龋水凝胶的制备方法主要分为物理交联法和化学交联法。物理交联法依靠非共价相互作用实现凝胶化,具有条件温和、生物相容性好的优势,是主要的封装手段。具体包括离子交联(如海藻酸钠与 Ca^{2+} 的配位络合)、温度诱导相变(如明胶、泊洛沙姆的温敏溶胶-凝胶转变)及pH响应性自组装等^[46]。相比之下,化学交联法则通过交联剂或通过光/热引发聚合反应构建共价键网络,可显著提升水凝胶的机械强度与结构稳定性,但需谨慎筛选交联剂种类和控制反应条件,以最大限度降低对菌体活性的损害^[47]。在众多选择中,京尼平作为一种天然交联剂,能与CS、明胶等材料中的氨基交联反应。由于其细胞毒性显著低于戊二醛等传统合成交联剂,能在强化凝胶网络的同时,最大限度地保持封装益生菌的生物活力^[48-49]。

益生菌的封装技术通常采用预混法(premixing method),即将益生菌(常为冻干菌粉或浓缩菌液)均匀分散于聚合物前体溶液中,再通过上述物理或化学交联方法实现原位凝胶化^[32]。该工艺的关键控制参数包括菌悬液浓度、混合均匀度及凝胶化速度,以确保菌体在三维凝胶网络中分布均匀,同时快速形成凝胶屏障以减少菌体在制备过程中的活性损失^[32,50]。此外,为应对口腔环境的复杂应力(如剪切力、低pH和酶解作用),研究者亦探索了乳液模板法、静电纺丝-复水法及喷雾干燥-复水凝胶化等进阶技术,以构建具有核-壳结构或多孔微载体的益生菌微胶囊,从而提供额外的物理化学屏障^[51]。

4. 水凝胶的理化性质调控

(1)凝胶强度、溶胀性与黏附性:水凝胶的凝胶强度、溶胀性和黏附性是其发挥防龋功能的关键物理性质。其中,凝胶强度主要依赖于聚合物浓度与交联密度的调控。足够的

机械强度可以使水凝胶抵抗口腔咀嚼力,维持结构完整性,从而有效保护内部封装的益生菌^[52]。然而,过高的交联密度可能会限制水分及营养物质的扩散,进而抑制益生菌的代谢活性^[53]。溶胀性反映了水凝胶吸收液体的能力。高溶胀性有利于吸收唾液,为益生菌输送营养物质并排出代谢产物^[54]。但过度溶胀可能导致凝胶结构松散甚至过早崩解,因此需要在溶胀率与结构稳定性之间寻求平衡^[55]。黏附性是延长水凝胶口腔滞留时间的关键。通过引入黏附性基团(如CS分子链上的氨基)^[56-57]或直接采用口腔黏附性聚合物(如卡波姆)^[58],可显著增强水凝胶对牙釉质或口腔黏膜的黏附能力,有效抵抗唾液冲刷,实现益生菌的局部长效滞留^[59]。

(2)响应性设计:响应性水凝胶经配方设计可兼顾菌体存活与定点释放,是实现益生菌智能递送、增强防龋靶向性的重要策略^[60]。pH响应型水凝胶通过基质缓冲抵御致龋菌产酸形成的酸性微环境($\text{pH} \approx 4.5$),在保护益生菌免受强酸损伤的同时,利用酸性条件诱导可离子化基团发生质子化或去质子化,触发溶胀降解并定点释放活菌^[61];温度响应型基于低临界溶解温度(lower critical solution temperature, LCST)特性,室温呈溶胶态便于高密度负载,至口腔温度(37°C)时发生亲水-疏水相转变及原位凝胶化,锁存菌体以抵抗唾液冲刷^[62];光响应型引入甲基丙烯酸酯基、偶氮苯等光敏基团,在特定波长光照下触发构象异构化,实现时空可控释放,避光时致密网络保障储存代谢稳定性^[63];酶响应型在交联键中嵌入基质金属蛋白酶(matrix metalloproteinase, MMP)特异性酶切肽,响应龋损区高表达的MMP降解交联位点,使凝胶在病灶区定位释菌,而健康非龋区域凝胶保持完整,持续维持菌体活性。各类响应性水凝胶的核心材料、响应机制及应用优势如表2所示。

(3)降解动力学与递送周期调控:水凝胶的降解动力学直接决定益生菌的释放速率与口腔有效治疗周期,其降解受基质性质、交联密度及口腔微环境(pH波动、酶解、唾液剪切)共同调控^[82]。天然高分子水凝胶(如壳聚糖、海藻酸钠)主要经酶促降解,交联密度与降解速率呈负相关,可实现最长4 d缓释,适用于短期干预^[83];其中纯壳聚糖在人工唾液中快速溶解,而海藻酸钠45 d内仅降解约40%^[84]。相比之下,

合成高分子水凝胶(如PEG衍生物)降解周期更长,通过调控交联密度与酯键密度可将活菌释放窗口延长至2~4周,满足慢性龋损的长效治疗需求^[85]。降解过快易致突释,过慢则可能阻碍营养扩散或诱发异物反应。因此,需通过天然-合成材料杂化或动态交联网络精准匹配降解与定植周期;酶响应型水凝胶则利用病灶特异性酶(如溶菌酶、MMP)介导的裂解,实现凝胶降解与菌体释放的同步调控,使给药周期与致龋生物膜的清除进程高度协同^[86]。

三、益生菌防龋水凝胶的作用机制

1. 物理屏障:水凝胶凭借高度交联的三维网络结构,在牙体硬组织与唾液的固液界面构筑一层致密的物理屏障,利用空间位阻效应,有效阻断外源性碳水化合物向牙面底层的渗透,从源头上抑制致龋菌的侵袭和早期生物膜形成^[70]。其效能核心在于界面黏附力(图1),例如CS-透明质酸聚合物体系不仅具备良好的组织相容性,还能与唾液黏蛋白产生特异性交互作用^[61]。这种仿生黏附机制使递送系统能够克服口腔冲刷,实现长期、稳固的靶向锚定,为后续益生菌的持续释放与定植提供空间保障。

2. 微环境调节:这是益生菌防龋水凝胶递送系统的核心生物学功能,旨在打破产酸-耐酸的致龋恶性循环,将高致病性的酸性微生态逆转为生理性的健康稳态。定植后的益生菌主要通过3种途径重塑局部微生态(图1)。
①竞争性排斥。益生菌可迅速锚定于牙面获得性膜(acquired pellicle, AP),通过物理占位抢占*S. mutans*等致龋菌的黏附位点。同时,在碳水化合物的摄取与发酵途径中展现出更高的代谢底物亲和力,从而切断致龋菌的营养供给。
②分泌抑菌物质。定植后的益生菌能够持续、缓慢地向微环境分泌多种拮抗物质,包括细菌素(如Reuterin^[87])、过氧化氢及有机酸。这些物质能在微米尺度的浓度梯度内有效抑制致龋菌生长并诱导部分菌株凋亡,且对正常共生菌群的干扰较小。
③pH值调控。部分益生菌(如唾液链球菌)携带有特定的酶系统,这部分菌群能高效水解唾液中的尿素代谢产氨,持续释放氢氧根离子,形成强大的微环境酸碱缓冲体系^[88],不仅直接阻断脱矿所需的临界酸性条件,还能从生态学角度诱导耐碱、产碱的健康共生菌富集,显著削弱致龋菌的生存竞争优势。

表2 不同响应类型防龋机制对比表

响应类型	触发因素	核心材料举例	主要响应机制	临床应用优势
pH响应型	局部酸性环境($\text{pH} \approx 4.5$)	聚丙烯酸(PAA)、壳聚糖(CS) ^[64] 、动态共价键(亚胺键) ^[65]	质子化/去质子化作用引起溶胀、收缩或降解 ^[66]	靶向酸性龋损病灶,实现药物精准释放 ^[67]
温度响应型	口腔体温($\approx 37^\circ\text{C}$)	泊洛沙姆(F127) ^[68] 、甲基纤维素 ^[69]	可逆溶胶-凝胶相转变(Sol-Gel) ^[70]	液体绷带:易于注入并快速原位固化 ^[71]
光响应型	特定波长(蓝光、近红外光) ^[72]	光敏蛋白 ^[72] 、含甲基丙烯酸酯基单体 ^[73]	光引发聚合 ^[73] 、光热效应 ^[74] 或光裂解 ^[75]	高时空分辨率,精准适配不规则龋洞 ^[76]
酶响应型	细菌分泌酶[基质金属蛋白酶(MMP)、葡萄糖基转移酶(Gtfs)] ^[77]	含MMP敏感肽段的聚乙二醇(PEG) ^[77]	酶切反应导致交联网络断裂或降解 ^[78]	关联病理状态,避免健康组织非特异性释放 ^[79]
多重响应型	多因素协同(如pH+温度)	接枝聚丙烯酸的泊洛沙姆(F127) ^[70]	逻辑门控,程序化释放	适配复杂动态微环境,提高治疗精准度 ^[80-81]

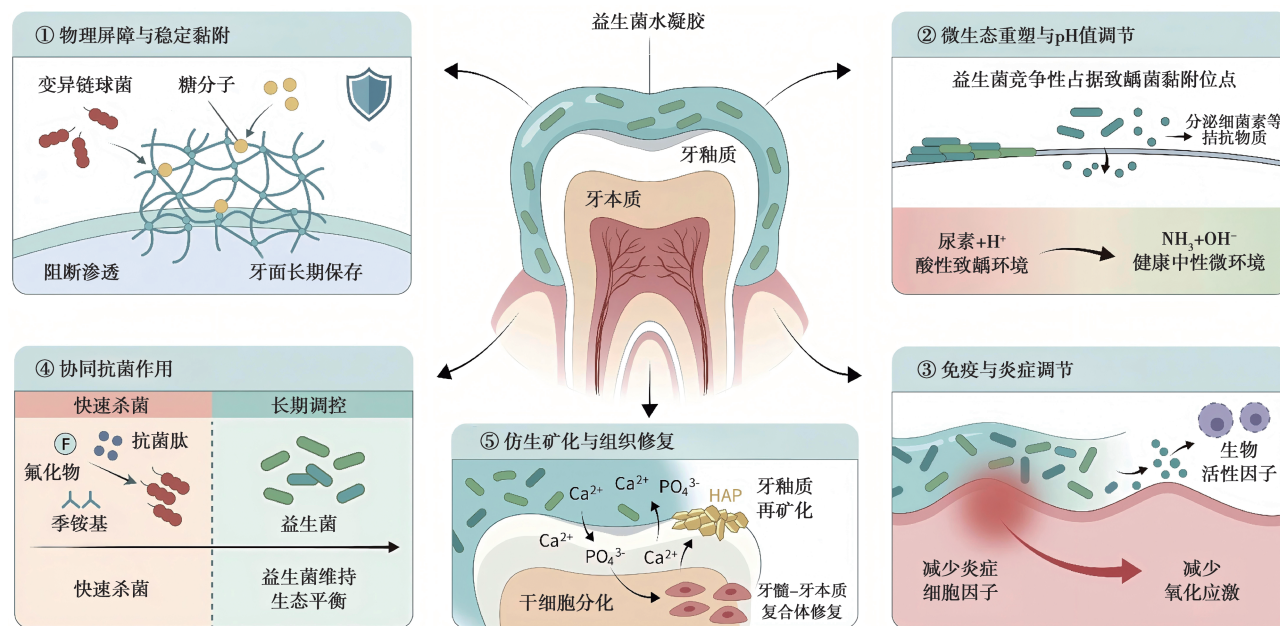


图1 益生菌水凝胶的防龋机制示意图 HAP:羟基磷灰石。

3. 免疫调节:在微环境调节的基础上,水凝胶系统还可发挥局部免疫与炎症调控作用(图1)^[89]。一方面,益生菌通过拮抗致龋菌,显著减少了致病性生物膜中内毒素、脂磷壁酸及其他毒性代谢产物的释放。病原基质的减少,直接下调了牙龈上皮细胞与成纤维细胞的炎症信号通路,间接降低了牙周及牙髓组织面临的局部炎症应激与氧化损伤^[90];另一方面,特定的水凝胶基质可被设计为智能响应型载体,共价结合或物理负载多种生物活性分子[如人β防御素3(human β-defensin 3, hBD3)等],不仅强化了局部的广谱抗感染能力,还能调节宿主天然免疫反应^[91],协同促进微生态环境的健康化。

4. 与其他抗菌成分的协同作用:在复合水凝胶体系中,益生菌与外源性抗菌成分(如氟化物、抗菌肽或天然植物提取物)及基质固有活性(如季铵化基团的静电杀菌作用^[92])形成了快慢结合的双重抑菌模式(图1)。在该协同体系中,外源性抗菌剂通常处于次要/辅助地位,负责及时干预(例如氟离子瞬时释放以抑制细菌糖酵解,迅速降低局部致龋菌丰度^[70]);益生菌则占据主要/核心地位,在抗菌剂削弱病原菌负荷后接管微环境,进行长效的生态调控^[93]。两者协同可在一定程度上兼顾急性抑菌与慢性微生态重建。

5. 牙体组织修复:水凝胶不仅作为递送载体^[94],更是矿化元素的控释储库(图1)。随着益生菌代谢调节使局部微环境趋于中性或弱碱性,水凝胶三维网络可精密调控钙、磷前驱体在脱矿界面的原位有序沉积,引导羟基磷灰石(hydroxyapatite, HAP)晶体外延生长,促进牙体硬组织的仿生再矿化进程^[95]。此外,特定基质可模拟牙体天然有机基质,负载hBD3、CTGF等生物活性分子诱导间充质干细胞分化,促进牙本质-牙髓复合体启动修复^[96],最终实现脱矿组织的功能性仿生再造。

四、当前挑战与展望

1. 临床转化技术性挑战:益生菌对理化压力极度敏感。传统灭菌手段(如γ射线)易造成细胞结构不可逆损伤,而冻干过程引发的渗透压冲击也会损害酶活性^[97]。虽然添加脱脂乳粉^[98]、海藻糖^[99]等保护剂能有效缓解损伤,但保护剂与特定凝胶基质的理化兼容性仍需优化。此外,室温(25℃)下菌株活力衰减迅速,如何突破冷链限制(如维持4或-18℃)以延长货架期仍是难题^[98]。除此之外,开发能够实时感知口腔pH值波动及酶浓度梯度的智能开关实现按需释放仍存在工艺难点^[100]。从温和无菌的实验室制备工艺向标准化、高重复性的工业级规模化生产过渡,仍是产品落地的瓶颈^[101]。

2. 临床操作性挑战:龋病好发于邻面、窝沟及根面等解剖结构复杂区域,传统涂布难以实现药物精准递送。针对邻面龋、根面龋等隐匿性病变,已有多种递送策略被开发^[102]:柔性微针贴片可穿透牙间隙,将水凝胶定向注入邻面靶区,在局部浓集给药的同时降低全身毒副作用^[103];具有剪切稀化特性的可注射水凝胶在剪切力下黏度骤降,易通过细针头注入狭窄间隙,撤力后迅速原位凝胶化,形成药物储库^[104]。在临床转化中,水凝胶的交联固化动力学与组织黏附强度是关键参数。理想防龋水凝胶需在2 min内快速原位成胶以抵抗口腔冲刷——光交联体系数十秒即可固化^[46],温敏体系在体温下数分钟内完成相转变^[43]。同时,其对牙面或黏膜的黏附强度应达10~20 kPa,以维持数小时至数天的病灶驻留,介导活性成分持续释放。增强黏附可通过界面设计引入静电、氢键、疏水作用及共价交联等多重相互作用实现。例如,透明质酸基活菌水凝胶经光引发原位交联后,凭借高黏附力维持益生菌长期定植,高效抑制致龋菌并促进组织修复^[48]。

3. 定植持久性挑战:口腔环境的高度动态性(唾液冲刷、

咀嚼、pH波动及微生物竞争)严重限制了益生菌的长期定植。动物实验证实,以1.0%结冷胶封装副干酪乳杆菌,可在小鼠口腔内实现长达10 d的有效定植^[32];临床研究亦表明,每日规律口服罗伊氏乳杆菌,能在2~4周内于唾液和牙菌斑中建立稳定定植窗口^[105]。为进一步延长口腔驻留时效,当前策略主要聚焦于3个方向。首先是益生元偶联策略,将益生菌与低聚果糖、菊粉等益生元协同配伍,为外源菌株提供原位碳源,竞争性阻断致龋病菌的生态位^[106];其次为菌株表型驯化与基因工程调控,通过压力驯化增强菌株对羟基磷灰石表面的亲和力,或利用基因工程靶向改造黏附基因,从而强化滞留效能^[107];最后是阶梯式给药方案,优化含服剂型,采用前期高剂量诱导定植、后期间歇维持补充的给药模式^[105]。

4. 益生菌长期使用的潜在风险:口腔微生态具有高度的个体特异性,不同人群的唾液成分与菌群结构会导致益生菌的定植效能出现显著差异^[108],单一配方难以适用所有人群。在引入外源性活菌群时,还需考虑是否会对口腔原有核心微生物组产生长期、不可预见的扰动^[109-110]。在口腔环境中,当宿主黏膜屏障发生破损或处于活动性炎症状态时,部分外源性益生菌(如乳杆菌属)可能跨越受损的上皮屏障发生异位易位与定植,并随消化道液体循环发生远端迁移,理论上具备诱发或加重胃肠道系统性病理损伤的潜在风险^[111]。此外,益生菌株亦被视为抗生素耐药基因(antibiotic resistance gene, ARG)的潜在宿主与储存库,其能够通过水平基因转移(horizontal gene transfer, HGT)机制,在同源菌群内部或向条件致病菌及临床病原菌扩散耐药表型,从而构成不容忽视的公共卫生安全风险^[112]。目前,多种益生菌联合使用或与抗菌剂共负载时,不仅其内部的拮抗或协同机制尚不完全明晰^[113],也缺乏标准化的安全评价体系。

5. 协同体系相容性挑战:在复合水凝胶递送体系中,益生菌与外源性抗菌组分(如氟化物、抗菌肽和植物提取物)常通过速释-缓释动力学耦合构建双重防龋机制。然而,抗菌组分的非特异性广谱杀伤效应易同步抑制益生菌活性,导致协同失效。目前主要有3种破解策略:一是时序控释程序设计,利用核-壳或多层微纳结构水凝胶实现差异化释放,抗菌剂先爆发式速释以迅速降低致龋菌负荷,待其浓度降至安全阈值后,益生菌再缓慢释放并定植,形成“先清除后重建”的级联协同效应^[79]。二是多维物理空间隔离工程,采用微胶囊技术(如壳聚糖/透明质酸自组装包覆结合明胶微球二次封装),借助不同降解动力学的屏障材料实现独立包裹,从物理上阻断抗菌组分与益生菌的直接接触与化学互作^[93]。三是益生菌生物抗性表型改造,通过定向驯化或基因工程增强益生菌株对特定抗菌剂(如氟化物)的耐受阈值,同时保持其原有抗龋功能与生物安全性^[114]。

6. 未来方向:未来,益生菌防龋水凝胶的发展应聚焦技术创新、机制深化与临床转化三大核心,重点突破以下研究方向:①智能响应体系升级,开发可实时感知口腔pH波动及酶浓度梯度变化的智能响应体系,实现益生菌的靶向释放与

病灶示警的双重功能^[115];②降解动力学的精准调控与个性化定制,建立基于个体口腔生理参数的降解动力学预测模型,开发可自调控降解速率的智能水凝胶^[70];③递送系统创新,通过益生菌表面工程改性与多层包覆技术,增强其在口腔环境中的抗逆性、靶向定植能力与存活周期^[116];④应用场景拓展,将应用范围从传统预防向根面龋等难治性病变延伸,推动水凝胶向抗菌、再矿化、菌群调控的集成化方向发展^[117];⑤临床转化推进,亟待开展高证据等级的随机对照试验(randomized controlled trial, RCT),积累临床循证医学证据,确立标准化给药规程与安全评价体系^[118]。

(1)人工智能(artificial intelligence, AI)在益生菌水凝胶设计中的应用:机器学习(machine learning, ML)为水凝胶设计提供了高效工具,可通过学习实验数据建立材料组成-性能-功能预测模型^[119]。以聚合物相对分子质量、交联密度和亲疏水性等为输入特征,ML模型可准确预测水凝胶的黏附强度与降解半衰期,指导配方优化^[120];贝叶斯优化与主动学习则可在生物约束下降低实验成本,加速凝胶化配方发现^[121]。在龋病微生态调控中,AI突破了多菌株筛选与释放试验的低效瓶颈^[122];组合筛选通过metaProbiotics语言模型结合宏基因组与主动学习,挖掘菌株协同/拮抗关系,实现双菌株配伍预测^[123];动力学预测利用径向基神经网络融合时空AI模型,整合载体特性与口腔微环境参数,精确拟合益生菌释放规律与定植周期,进而指导基质优化以延长病灶滞留时间^[124]。

(2)拓展应用场景:固定正畸、舍格伦综合征及放化疗口干症患者均为龋病高危人群,据此开发定制化益生菌水凝胶系统是当前口腔防龋制剂的前沿方向。正畸附件易致菌斑滞留且游离益生菌易被冲刷,基于结冷胶的高黏附水凝胶可紧密填充矫治间隙,实现菌体局部长效缓释,持续抑制*S. mutans*增殖^[125]。口干症患者因唾液流速与缓冲能力严重不足,致龋菌恶性富集;定制化水凝胶搭载防龋乳杆菌并复配海藻酸钠、木糖醇等保湿组分,可协同益生菌缓释与局部润湿效应,纠正口腔微生态失衡,遏制恶性龋的发生发展^[126]。然而,上述专用制剂研究仍多限于体外评价与小样本试验,宿主菌群的内在异质性已成为制约其标准化临床转化的核心因素^[50]。

五、结论

益生菌防龋水凝胶的兴起,推动龋病干预策略从传统的被动修复向主动调控转变。体外研究显示,该体系通过物理屏障阻绝、口腔微环境重塑、多靶点协同抗菌、促进硬组织再矿化及微生态重建等多机制有机耦合,最终实现拮抗核心致龋菌与重建口腔微生态平衡的双重目标。然而,现有研究仍多局限于体外理化评价与材料设计,缺乏充分的体内证据以证实其生物安全性与防龋效能,与临床转化间存在明显鸿沟;该体系在个体口腔微环境中的原位定植动力学、长期稳定性及时空干预效能,仍亟待体内模型系统验证。未来,该体系应向精准定制诊疗迭代,基于宿主菌群特征制定干预策略,这一目标的实现亟待材料学、微生物学与口腔医学的深

度交叉,后续研究需聚焦体内外关联性研究、标准化动物模型验证及严格的循证医学评价,通过积淀核心临床前证据,为龋病高效防控提供坚实的科学支撑。

利益冲突 所有作者均声明不存在利益冲突

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