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乳杆菌与龋病关系的研究进展*

张 瑾，徐 欣△

口腔疾病研究国家重点实验室 国家口腔疾病临床医学研究中心 四川大学华西口腔医院 牙体牙髓病科（成都 610041）

【摘要】 乳杆菌是最早发现的龋病相关微生物，具有产酸性、耐酸性及结合胶原蛋白和合成细胞外多糖促进细菌黏附的能力。部分乳杆菌可产生抗菌物质或代谢物、与致龋菌竞争黏附位点或共聚、调节致龋毒力相关基因表达，从而抑制致龋菌生长，因此近年来有研究将乳杆菌作为益生菌应用于龋病防控。但乳杆菌致龋机制尚不明确，特定“益生”乳杆菌对口腔和肠道微生态的潜在影响未知，尚需更多的研究结合乳杆菌的致龋性和益生性，综合评价其对口腔和全身健康和疾病的作用。本文旨在对近年来乳杆菌致龋性和防龋作用的相关研究进行综述，重点讨论乳杆菌在龋病发生发展与临床防控中的作用，为龋病的防控提供新的思路和参考。

【关键词】 乳杆菌 龋病 益生菌 变异链球菌

Research Progress in the Relationship Between *Lactobacillus* and Dental Caries

ZHANG Jin, XU Xin△. *State Key Laboratory of Oral Diseases, National Clinical Research Center for Oral Diseases, Department of Cariology and Endodontics, West China Hospital of Stomatology, Sichuan University*, Chengdu 610041, China

△ Corresponding author, E-mail: xin.xu@scu.edu.cn

【**Abstract**】 *Lactobacillus* is the first microorganism found to be closely associated with dental caries. It demonstrates acidogenicity, aciduricity, and the ability to bind with collagen and to synthesize extracellular polysaccharides to promote bacterial adhesion. Some lactobacilli inhibit the growth of cariogenic bacteria by producing antibacterial compounds or metabolites, competing with cariogenic bacteria for adhesion sites or co-aggregation, or regulating the expression of genes related to cariogenic virulence. Therefore, researchers have, in recent years, experimented with applying *Lactobacillus* as probiotics in the prevention and control of caries. However, the cariogenic mechanism of *Lactobacillus* is still not fully understood, and the potential effects, presumably beneficial, of specific *Lactobacillus* on oral and intestinal microecology remain unknown. More research needs to be done to combine both the cariogenic and probiotic properties of *Lactobacillus*, and to comprehensively evaluate the effects of *Lactobacillus* on oral and systemic health. We, herein, summarized research progress in the cariogenicity and caries prevention effect of *Lactobacillus*, focusing on a discussion of the role of *Lactobacillus* in cariogenesis, the development of dental caries, and clinical prevention and control of dental caries, in order to provide new ideas and references for the prevention and control of dental caries.

【**Key words**】 *Lactobacillus* Dental caries Probiotic *Streptococcus mutans*

龋病是由细菌为主的多种因素所引起的牙体硬组织进行性破坏的疾病，是人类最常见的慢性疾病之一[1]。乳杆菌（*Lactobacillus*）是一群革兰阳性、兼性厌氧或微好氧的杆状且无芽孢的细菌，参与构成人体多个部位的微生物区系，如消化系统、泌尿系统和生殖系统[2]。在口腔内，乳杆菌大量存在于唾液、舌背、黏膜和硬腭，少数存在于牙面[3]。唾液中常见的乳杆菌包括嗜酸乳杆菌（*Lactobacillus acidophilus*）、干酪乳杆菌（*Lactobacillus casei*）、发酵乳杆菌（*Lactobacillus fermentium*）、副干酪乳杆菌（*Lactobacillus paracacei*）、植物乳杆菌（*Lactobacillus plantarum*）、鼠李糖乳杆菌（*Lactobacillus rhamnosus*）和唾液乳杆菌（*Lactobacillus salivarius*）等[4]。乳杆菌是最早发现的龋病相关微生物，其与龋病之间关系的研究可追溯到20世纪上半叶[1, 5]。然而近年来，多项体内外研究发现部分乳杆菌具有防龋作用。鼠李糖乳杆菌GG可降低儿童龋齿的发病率[6]。鼠李糖乳杆菌GG和干酪乳杆菌Shirota可以减少变异链球菌对羟基磷灰石的黏附[7]。此外，鼠李糖乳杆菌LB21促进根面龋的再矿化[8]。植物乳杆菌299v、罗伊氏乳杆菌SD2112、罗伊氏乳杆菌PTA 5289和鼠李糖乳杆菌GG能干扰变异链球菌生物膜形成[9]。因此乳杆菌在龋病发生发展和防治中的作用具有两面性。本文对近年来乳杆菌致龋性和防龋作用的相关研究进行综述，旨在为龋病的防控提供新的思路和参考。

1 乳杆菌的致龋性

乳杆菌不是龋病的始发致病菌，但在龋病进展中发挥重要作用[10]。成人唾液和龋损部位的乳杆菌计数与恒牙龋失补指数正相关，龋活跃患者唾液乳杆菌计数显著

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△ 通信作者，E-mail: xin.xu@scu.edu.cn

高于无龋患者,且龋损部位乳杆菌水平较唾液乳杆菌水平高[11]。学龄前有龋儿童口腔中乳杆菌检出率显著高于无龋儿童[12]。口内检出发酵乳杆菌的儿童,其deft、dt、defs和ds评分高于未检出发酵乳杆菌的儿童[13]。乳杆菌与龋病发生发展密切相关,但乳杆菌致龋机制尚不明确,可能与其产酸性、耐酸性和黏附性有关。

1.1 产酸性和耐酸性

乳杆菌产生乳酸作为碳水化合物发酵的主要终产物[14]。乳酸使牙面局部pH值降低至4.5以下,酸化的口腔微环境导致牙菌斑内微生物种群向更加产酸和耐酸的微生物演替,当牙面pH值持续低于脱矿的临界pH值(5.5)时,牙体硬组织脱矿与再矿化之间的平衡被打破,龋病由此发生发展[15-16]。由于代谢和碳水化合物发酵能力的差异,乳杆菌菌株间产酸能力明显不同,唾液乳杆菌、鼠李糖乳杆菌、植物乳杆菌、干酪/副干酪乳杆菌的产酸性较强[17]。其中,唾液乳杆菌是产酸最快的乳杆菌菌株之一,其在蔗糖存在时可显著降低牙菌斑pH值并改变微群落结构,产酸性与致龋表型相一致[17]。乳杆菌在强酸环境下生长更具竞争力,当暴露于pH值为4的酸性环境时,非变异链球菌和放线菌普遍出现生长延迟和活力丧失的现象,而乳杆菌耐受酸性环境[18],甚至在pH值低至2.2时仍能存活[19]。PIWAT等[17]发现乳杆菌的生长速率与pH值降低呈正相关。CHEN等[20]首次证明*Lactobacillus sakei*表现出与变异链球菌相似的产酸性和耐酸性,其代谢蔗糖产酸使pH值降至4 ~ 5,在pH值为3.5的环境中暴露60 min后存活率约65%。

1.2 黏附性

乳杆菌不易黏附于牙面,当变异链球菌和/或其他早期定植者创造一个富含碳水化合物的酸性环境时,乳杆菌能定植在该生态位中并迅速生长[21]。疏水相互作用是微生物黏附于表面的主要决定因素,乳杆菌细胞表面疏水性调节其黏附作用[22]。嗜酸乳杆菌、短乳杆菌(*Lactobacillus brevis*)和卷曲乳杆菌(*Lactobacillus crispatus*)等细胞壁上存在S层蛋白,根据外界环境变化改变细菌表面疏水性[23-24]。嗜酸乳杆菌M92、卷曲乳杆菌JCM 5810等的S层蛋白介导细菌与宿主细胞或细胞外基质蛋白黏附,或具有保护功能[25]。牙本质由羟磷灰石无机物和主要为Ⅰ型胶原蛋白的细胞外有机基质组成[26]。细菌产酸使牙齿脱矿,暴露牙本质中的胶原蛋白,这些胶原蛋白是细菌胶原酶和胶原结合蛋白的靶标[27]。鼠李糖乳杆菌、副干酪乳杆菌和植物乳杆菌等可以结合Ⅰ型胶原蛋白帮助它们在牙本质龋损中定植[13]。从重度低龄儿童龋患儿口内可分离得到干酪乳杆菌、鼠李糖乳杆菌、发酵乳杆菌、唾液乳杆菌等,它们的基因组中含有与胶原结合蛋白相关的基因[21]。LEHRI等[28]发现发酵乳杆菌3872的胶原结合蛋白可以与胃肠道内壁上皮细胞表面的Ⅰ型胶原蛋白结合,从而抑制胃肠道病原体空肠弯曲杆菌与Ⅰ型胶原蛋白的结合。

细胞外多糖(extracellular polysaccharides, EPS)介导微生物对牙面及微生物之间的黏附[29]。嗜酸乳杆菌、干酪乳杆菌和鼠李糖乳杆菌产生EPS促进细菌黏附并增强细菌对复杂环境和宿主防御的抵抗力[30]。副干酪乳杆菌BGNJ1-64和鼠李糖乳杆菌GG具有与碳水化合物转运和代谢及EPS合成有关的基因,能与黏蛋白、胶原和上皮细胞结合,在微生物黏附和生物膜形成中有重要作用[31-32]。植物乳杆菌VAL6的*cps4E*、*cps4F*及约氏乳杆菌(*Lactobacillus johnsonii*)FI9785的*epsE*(*cps4E*)编码葡糖基转移酶,分别将糖核苷酸或半乳糖-1-磷酸运输至脂质载体以调节EPS的合成[33]。鼠李糖乳杆菌调节EPS合成的*wzb*基因在牙本质活动期和静止期龋损中差异表达,提示该基因可能在龋病进展中发挥重要作用[34]。重度低龄儿童龋患儿口内乳杆菌基因组中大多含有蔗糖特异性磷酸转移酶系统的EII组分、蔗糖6-磷酸水解酶和蔗糖磷酸化酶[21]。

2 乳杆菌的防龋作用

植物乳杆菌FB-T9能抑制变异链球菌生长,破坏变异链球菌生物膜结构,动物实验表明,植物乳杆菌FB-T9可以定植于大鼠口腔,显著降低磨牙牙面变异链球菌的数量和龋齿评分[35]。ZHANG等[36]经大鼠体内实验发现植物乳杆菌CCFM8724显著抑制变异链球菌和白色念珠菌(*Candida albicans*)在口内定植,减少大鼠下颌磨牙牙釉质脱矿并降低龋齿分数,其抑菌和抗龋作用甚至优于0.02%的氯己定。SANDOVAL等[37]让2 ~ 3岁儿童在工作日每天饮用添有鼠李糖乳杆菌SP1的牛奶,10个月后,这些儿童口内龋齿数显著低于饮用普通牛奶的儿童,表明学龄前儿童定期饮用添有鼠李糖乳杆菌SP1的牛奶可降低龋齿发病率。RODRIGUEZ等[38]评估了添加有鼠李糖乳杆菌GG的牛奶和普通牛奶对智利学龄前儿童龋齿的影响,10个月后,鼠李糖乳杆菌GG牛奶组和普通牛奶组儿童患龋率分别为54.4%和65.8%,龋齿发病率分别为9.7%和24.3%,表明长期定期摄入含有鼠李糖乳杆菌GG的牛奶可以减缓高龋风险儿童龋齿的发展。LIN等[39]报道副干酪乳杆菌副干酪亚种NTU 101(*Lactobacillus paracasei subsp. Paracasei* NTU 101, NTU 101)对变异链球菌、白色念珠菌、粪肠球菌(*Enterococcus faecalis*)等均有抑菌活性。目前研究表明,乳杆菌的防龋机制主要包括产生抗

菌物质或代谢物抑制致龋菌生长、与致龋菌竞争黏附位点或共聚及调节致龋毒力相关基因的表达。

3　乳杆菌的防龋机制

3.1　产生抗菌物质或代谢物抑制致龋菌生长

部分乳杆菌可以产生细菌素、有机酸、过氧化氢等抗菌物质或代谢物抑制致龋菌生长[40]。从无龋学龄前儿童口中分离得到的副干酪乳杆菌SD1具有多种益生活性，包括抑制变异链球菌生长、黏附于口腔上皮细胞、合成细菌素及升高唾液人中性粒细胞肽(human neutrophil peptide, HNP)1-3调节免疫等[41]。MANMONTRI等[42]发现学龄前儿童每天或每周三次食用含副干酪乳杆菌SD1的奶粉显著减少唾液和牙菌斑中变异链球菌数量，该结果在停用此奶粉后可维持至少6个月。另一项研究[43]中，20名青少年每天食用含副干酪乳杆菌SD1的奶粉6个月，与对照组相比，副干酪乳杆菌组唾液中总乳杆菌和副干酪乳杆菌/干酪乳杆菌水平显著升高，总链球菌和变异链球菌水平显著降低，但细菌总体水平无明显变化。副干酪乳杆菌SD1的抑菌机制可能源于其产生的细菌素Paracasin SD1，Paracasin SD1在较宽的pH范围(3～8)内对致龋菌如变异链球菌和表兄链球菌(*Streptococcus sobrinus*)、牙周致病菌如伴放线聚集杆菌(*Aggregatibacter actinomycetemcomitans*)和牙龈卟啉单胞菌(*Porphyromonas gingivalis*)及白色念珠菌均有较强的抗菌活性，并不受α-淀粉酶、过氧化氢酶和唾液的影响[44-45]。罗伊氏乳杆菌在厌氧条件下发酵甘油产生罗伊氏菌素(reuterin)，罗伊氏菌素对细菌、病毒和真菌均有生物活性，可能由于其与蛋白质的巯基发生反应或与核糖核苷酸特异性竞争结合位点，从而抑制微生物DNA合成[46]。YANG等[47]研究发现罗伊氏乳杆菌AN417培养上清液可显著降低变异链球菌的生长速度、细胞内ATP水平、细胞活力等，同时破坏变异链球菌生物膜的完整性，添加脂肪酶或α-淀粉酶的培养上清液失去对变异链球菌的抑菌作用，表明培养上清液中的抗菌物质可能是脂肪酸和/或碳水化合物的代谢物。植物乳杆菌K25显著降低变异链球菌的黏附率并抑制其生长及生物膜形成，添加乳酸或过氧化氢酶的植物乳杆菌K25培养上清液对变异链球菌的抑菌作用增强或减弱，提示植物乳杆菌K25的抑菌机制可能与代谢过程中合成的乳酸和过氧化氢有关[48]。

3.2　与致龋菌竞争黏附位点或共聚

黏附是细菌定植于口腔的先决条件，乳杆菌附着在口腔黏膜或牙齿表面可以竞争变异链球菌等致龋菌的结合位点，限制它们生长和生物膜形成[49]。乳杆菌与变异链球菌共聚集可防止变异链球菌与可能形成牙菌斑生物膜的表面结合，且有利于从口腔中快速清除变异链球菌[50]。CIANDRINI等[51]证明副干酪乳杆菌B21060和鼠李糖乳杆菌ATCC 53103及它们无细胞的培养上清液能抑制变异链球菌和口腔链球菌生物膜形成，副干酪乳杆菌B21060与口腔链球菌、鼠李糖乳杆菌ATCC 53103与变异链球菌具有良好的共聚集能力，共聚集率分别为23.50%和20.93%。FANG等[6]发现从健康人牙菌斑中分离得到的短乳杆菌BBE-Y52对变异链球菌具有抗菌活性，其产酸能力较变异链球菌和唾液乳杆菌弱，而耐酸性较干酪乳杆菌和副干酪乳杆菌强，短乳杆菌BBE-Y52能与变异链球菌共聚集，抑制变异链球菌生物膜形成和自聚集，并具有黏附于口腔上皮细胞的能力。短乳杆菌KU15153是从泡菜中分离得到的益生菌，其耐受人工胃环境，对抗生素敏感，对食源性致病菌如大肠杆菌、金黄色葡萄球菌和鼠伤寒沙门氏菌等具有一定的抗菌活性[52]。JIANG等[53]证明短乳杆菌KU15153对变异链球菌同样具有抗菌活性，并通过降低变异链球菌的自聚集性、细胞表面疏水性和EPS的产生来抑制生物膜形成。ZHANG等[54]发现植物乳杆菌K41抑制变异链球菌生长、EPS和生物膜的形成，植物乳杆菌K41与变异链球菌共聚集率约40%。每日用植物乳杆菌K41菌液在高糖饮食大鼠磨牙区涂拭，5周后大鼠磨牙龋齿的发病率和严重程度较对照组显著降低[54]。

3.3　调节致龋毒力相关基因的表达

WASFI等[55]发现干酪乳杆菌ATCC 393、罗伊氏乳杆菌ATCC 23272、植物乳杆菌ATCC 14917及唾液乳杆菌ATCC 11741对变异链球菌表现出pH依赖性的抗菌和抗生物膜作用，它们的培养上清液下调变异链球菌毒力相关基因的表达，如合成EPS的基因*gtfBCD*、耐酸基因*atpD*、群体感应基因*comCD*及*vicRK*等。副干酪乳杆菌28.4是无龋个体的口腔分离株，掺入结冷水凝胶(gellan hydrogel)材料中的副干酪乳杆菌28.4具有抗变异链球菌及其生物膜的作用，并抑制EPS合成及致龋毒力相关基因*luxS*、*brpA*、*gbpB*、*gtfB*的表达[56]。*Lactobacillus kefiranofaciens* DD2的培养上清液抑制变异链球菌和表兄链球菌的生长和生物膜形成，且下调与生物膜形成及碳水化合物代谢相关的基因，如*brpA*、*comDE*、*vicR*、*gbpB*、*spaP*和*ftf*[57]。变异链球菌和白色念珠菌在生物膜中共生存在，变异链球菌合成葡聚糖紧密结合白色念珠菌，白色念珠菌促进变异链球菌微菌落的发展，导致高致龋性双菌种生物膜形成[58]。SRIVASTAVA等[59]发现植物乳杆菌108的培养上清液可抑制变异链球菌和白色念珠菌的单、

双菌种生物膜形成,并破坏成熟生物膜微结构,生物膜中葡萄糖转移酶基因*gtfB*、*gtfC*、*gtfD*和菌丝特异性基因*HWP*1、*ALS*1、*ALS*3在植物乳杆菌108的上清液中表达减少。

4 总结与展望

前期多项流行病学研究结果支持乳杆菌致龋这一观点,唾液乳杆菌检测也因此被列为龋病风险评估的重要内容。发酵乳杆菌、嗜酸乳杆菌长期以来被视为口腔致龋菌,其他乳杆菌如*Lactobacillus sakei*、副干酪乳杆菌BGNJ1-64等因表现出与变异链球菌相似的产酸性、耐酸性或黏附性,具有致龋活性。近年来针对乳杆菌黏附与耐酸相关分子机制的研究取得了较大进展,但相较于口腔另一经典致龋菌——变异链球菌,其致病机制及其与口腔微生态系内其他微生物的交互作用仍有待深入研究,亟待通过临床队列研究结合体外多菌种模型和动物实验模型验证,锁定乳杆菌关键致龋毒力菌株及其毒力调控关键因子和通路,以期为龋病的临床防治提供潜在靶点。

随着近年来微生态制剂在调控肠道微生态、防治全身系统性疾病中的应用与机制研究的进展,特定乳杆菌株作为口腔益生菌调控口腔微生态平衡,进而防治龋病等多种口腔感染性疾病已成为口腔疾病防治领域的热点。近期研究发现,副干酪乳杆菌SD1、罗伊氏乳杆菌AN417、植物乳杆菌K25能抑制致龋菌生长,副干酪乳杆菌B21060、鼠李糖乳杆菌ATCC 53103、短乳杆菌BBE-Y52等能与致龋菌竞争黏附位点或共聚,干酪乳杆菌ATCC 393、*Lactobacillus kefiranofaciens* DD2、植物乳杆菌108等可以下调细菌致龋毒力,从而起到潜在的防龋作用。值得注意的是,特定乳杆菌株作为益生菌,在干预期间或干预后可能只是短暂停留于口腔,目前尚缺乏有力证据表明经口腔摄入的乳杆菌可长期稳定的定植于口腔生态系内[60]。此外,外源性摄入"益生"乳杆菌株对口腔及肠道微生态可能产生的双重影响,及其对口腔与全身健康和疾病防治的作用有待进一步综合评价。根据乳杆菌的致龋性和益生性选择合适的菌株,进一步明确其剂量、周期、载体及其对口腔与全身疾病防治的效能与卫生经济学效益等,建立临床共识与标准,将是当前应用乳杆菌防控龋病以及其他口腔感染性疾病所面临的重要挑战和亟待解决的关键问题。

* * *

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