

## 益生菌防治牙周疾病及种植体周围疾病的研究进展

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**【摘要】** 益生菌参与调节宿主的各个微生态系统, 具有治疗多种生态失调相关疾病的潜在可能。近年来研究发现, 益生菌在口腔疾病特别是牙周疾病的防治中具有良好的应用前景, 然而目前益生菌在生物医学领域中的潜能尚未被完全开发。本文通过文献回顾, 对益生菌在口腔疾病, 特别是牙周疾病和种植体周围疾病防治中的作用机制、效果和临床应用前景作一综述。

**【关键词】** 益生菌; 牙周病; 种植体周围疾病; 牙周致病菌

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### Research progress on probiotics for the prevention and treatment of periodontal disease and peri-implant disease

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**【Abstract】** Probiotics participate in the regulation of various micro-ecosystems of the host and have the potential to treat a variety of diseases related to microecological imbalance. In recent years, some studies have found that probiotics have a good application prospect in the prevention and treatment of oral diseases, especially periodontal diseases, however, the potential of probiotics in the biomedical field has not been fully developed. This paper is to review the mechanism, effect, and application prospect of probiotics in the prevention and treatment of oral diseases, especially periodontal diseases and peri-implant diseases.

**【Key words】** Probiotics; Periodontal diseases; Peri-implant disease; Periodontal pathogens

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益生菌是指通过宿主免疫调节及菌群调节保护机体健康的微生物<sup>[1]</sup>。目前, 慢性牙周炎的治疗主要是以牙周基础治疗为主, 包括口腔卫生宣教、龈上洁治、龈下刮治及根面平整(scaling and root planning, SRP), 去除局部刺激因素, 达到减少相关临床指标的目标, 包括减少探诊深度(probing depth, PD)、临床附着丧失(clinical attachment loss, CAL)、探诊出血(bleeding on probing, BOP)、菌斑指数(plaque index, PLI)和牙龈指数(gingival index, GI)等。抗生素可辅助牙周治疗, 但由于其具有全身性不良反应、胎毒性, 且会促进新的耐药菌株产生, 影响其使用的安全性<sup>[2]</sup>。而益生菌无细胞毒性, 且具有良好的抗菌性和抗炎性<sup>[3]</sup>, 是替代抗生素辅助治疗口腔疾病的新方法。本文旨在阐述益生菌在口腔疾病, 特别是在牙周疾病和种植体周围疾病防治中的作用机制与应用现状, 为益生菌的相关研究提供思路。

#### 一、益生菌防治口腔疾病的机制

目前, 用于治疗口腔疾病的益生菌主要包括乳杆菌和双歧杆菌, 还包括少量的酵母菌和链球菌等。其中乳杆菌包括罗伊氏乳杆菌(*Lactobacillus reuteri*)、格氏乳杆菌(*Lactobacillus gasseri*)、干酪乳杆菌(*Lactobacillus casei*)、鼠李糖乳杆菌(*Lactobacillus rhamnosus*)、植物乳杆菌(*Lactobacillus plantarum*)、发酵乳杆菌(*Lactobacillus fermentum*)和短乳杆菌(*Lactobacillus brevis*)等; 双歧杆菌主要包括两歧双歧杆菌(*Bifidobacterium bifidum*)、长双歧杆菌(*Bifidobacterium longum*)、短双歧杆菌(*Bifidobacterium breve*)、动物双歧杆菌(*Bifidobacterium animalis*)等, 除乳杆菌和双歧杆菌外还包括乳酸片球菌(*Pediococcus acidilactici*)、乳酸链球菌(*Streptococcus lactis*)等其他菌属<sup>[4]</sup>。这些益生菌主要通过免疫调节、下调炎症级联反应和抑制病原菌, 来防治口腔炎症疾病。

益生菌通过不同途径调节免疫系统, 如增强黏膜屏障功能<sup>[5]</sup>, 影响巨噬细胞对病原相关模式分子的识别, 或通过相关信号通路增加抗炎细胞因子, 减少促炎细胞因子<sup>[6]</sup>。鼠李糖乳杆菌和动物双歧杆菌乳亚种(*Bifidobacterium animalis* subsp. *lactis*)黏附在牙龈上皮细胞上, 增强屏障作用, 减弱牙龈卟啉单胞菌(*Porphyromonas gingivalis*)对牙龈上皮细胞的黏附和侵袭, 调节天然免疫, 降低牙龈卟啉单胞菌对细胞活

力的影响,降低肿瘤坏死因子(tumor necrosis factor, TNF)、白细胞介素(IL)-1水平,增加IL-8分泌,下调Toll样受体(Toll-like receptors, TLR)-4表达<sup>[7]</sup>。益生菌还可通过调节防御细胞的表型影响炎症,嗜酸乳杆菌(*Lactobacillus acidophilus*)通过促进IL-1 $\beta$ 等炎症因子的正向调节增加牙周组织天然防御的抗菌活性<sup>[8]</sup>。大鼠实验显示,动物双歧杆菌乳亚种HN019含片能调节牙周组织的免疫炎症参数,显著降低牙周炎的严重程度<sup>[9]</sup>。短乳杆菌产生精氨酸脱氨酶,从而抑制了一氧化氮合酶,降低一氧化氮的产生,发挥抗炎作用<sup>[10]</sup>。

益生菌还可通过抑制病原菌重建口内微生物群<sup>[11]</sup>。研究发现,益生菌分泌抗微生物的复合物和细菌素,破坏致病菌的细胞壁,降低生物膜pH值,改善微生态内微生物组成<sup>[12]</sup>。益生菌与致病菌竞争营养物,抑制牙周致病菌增殖,口服乳杆菌使龈下菌斑的牙龈卟啉单胞菌、福赛斯坦纳菌(*Tannerella forsythia*)、中间普氏菌(*Prevotella intermedia*)、齿垢密螺旋体(*Treponema denticola*)、伴放线菌聚集菌(*Aggregatibacter actinomycetemcomitans*) 5种牙周致病菌数量总和显著减少<sup>[13-14]</sup>。

## 二、益生菌在牙周疾病防治中的应用

益生菌在牙周疾病的应用主要集中在乳杆菌,慢性牙周炎患者与健康人口腔杆菌群组成存在差异。健康人唾液中最常见的益生菌菌株是格氏乳杆菌和发酵乳杆菌,慢性牙周炎患者中最常见的菌株是植物乳杆菌<sup>[6]</sup>。Köll-Klais等<sup>[15]</sup>研究发现,体内检出的乳杆菌对牙周致病菌及龋病相关链球菌均有一定抑制作用,具有菌株差异性;在健康人与慢性牙周炎患者间乳杆菌的检出量差异无统计学意义,且龈下检出均很少。

益生菌在治疗牙周疾病方面的应用方式主要是含片<sup>[16]</sup>、漱口水<sup>[17]</sup>、牛奶<sup>[18]</sup>、口香糖<sup>[19]</sup>和牙膏<sup>[20]</sup>等的添加物,通过口腔接触,影响口腔内微生态及临床表现。

1. 牙龈炎:关于益生菌应用于牙龈炎的治疗是否有效,目前研究的结论尚未完全一致。部分研究认为益生菌有助于改善牙龈状况,临床试验证明乳杆菌可改善牙龈炎的PLI和BOP等临床指标<sup>[21]</sup>。Montero等<sup>[22]</sup>应用植物乳杆菌、短乳杆菌和乳酸片球菌3种益生菌含片显著减少龈下福赛斯坦纳菌含量。Schlagenhauf等<sup>[23]</sup>研究提示,口服罗伊氏乳杆菌含片可减少牙周临床指数,有效治疗妊娠期牙龈炎。然而,也有研究表示仍需要更多实验数据佐证益生菌对牙龈炎症及口腔微生态环境的改善作用<sup>[24]</sup>。研究结果的差异性和益生菌菌株的种类、益生菌的含量、剂型的选择、服用的频率、实验模型及对受试者的选择等因素相关。

2. 慢性牙周炎:益生菌在慢性牙周炎患者的临床治疗中可能有良好的效果。Radaic等<sup>[25]</sup>的体外实验发现,乳酸乳球菌(*Lactococcus lactis*)及其抗菌肽Nisin可有效抑制含有牙周致病菌的生物膜的生长。Alshareef等<sup>[26]</sup>的临床研究指出,与单纯采取牙周基础治疗相比,使用包含了嗜酸乳杆菌、干酪乳杆菌、两歧双歧杆菌、鼠李糖乳杆菌和唾液乳杆菌(*Lactobacillus salivarius*)的益生菌含片的患者出血指数显著降低。罗伊氏乳杆菌辅助牙周基础治疗的患者PD和牙龈卟啉单胞菌的数量都显著降低<sup>[16]</sup>。Laleman等<sup>[27]</sup>报道,口服重

组短乳杆菌含片可以显著减少牙周炎患者的深牙周袋数量,降低平均PD,在具有中等(4~6 mm)和深(>6 mm)牙周袋的牙周炎患者中更为显著。Jansen等<sup>[28]</sup>发现,唾液链球菌(*Streptococcus salivarius*)K12和M18的纯培养物对牙龈卟啉单胞菌和具核梭杆菌(*Fusobacterium nucleatum*)均有抑制效果。含乳杆菌和双歧杆菌的牙膏减少了中间普氏菌、具核梭杆菌等牙周致病菌<sup>[20]</sup>。

## 三、益生菌在种植体周围疾病防治中的应用

种植体周围疾病分为种植体周围黏膜炎和种植体周围炎,发病率分别为43%和22%<sup>[29]</sup>。由于罗伊氏乳杆菌对牙龈卟啉单胞菌、中间普氏菌、唾液链球菌和金黄色葡萄球菌(*Staphylococcus aureus*)具有抗菌效应<sup>[14]</sup>,目前有文献支持益生菌有助于改善种植体周围疾病。Galofré等<sup>[30]</sup>发现,罗伊氏乳杆菌可改善种植体周围黏膜炎和种植体周围炎的PD和BOP。临床研究证明,种植体周围炎患者服用罗伊氏乳杆菌12、24周后PLI和BOP比安慰剂组显著降低<sup>[31]</sup>。Alqahtani等<sup>[32]</sup>报道,不吸烟者在3个月的随访中接受罗伊氏乳杆菌含片辅助SRP患者的BOP和PLI的减少量显著高于仅接受SRP患者。益生菌也有助于改善健康人群的临床参数,用于种植体周围黏膜炎的防治,临床研究发现健康人群和种植体周围黏膜炎患者口服罗伊氏乳杆菌30 d后,龈沟液量、PLI、PD、GI,以及IL-1 $\beta$ 、IL-6和IL-8的下降幅度均显著高于安慰剂组<sup>[33]</sup>。

另有研究对益生菌的积极效应产生质疑,认为乳杆菌对种植体周围病的临床改善益处有限<sup>[34]</sup>。Mongardini等<sup>[35]</sup>报道,使用植物乳杆菌和短乳杆菌并没有显著提高菌斑清除和光动力疗法治疗种植体周围黏膜炎的临床效果。Zhao等<sup>[36]</sup>研究显示,短期内使用乳杆菌联合SRP与单用SRP相比不能显著改善PLI和BOP。Peña等<sup>[37]</sup>也发现,在SRP和使用0.12%氯己定含漱液后服用3个月的罗伊氏乳杆菌与单独使用SRP和0.12%氯己定含漱液相比没有显著作用。

目前,益生菌在治疗种植体周围疾病的应用效果还存在较大的争议<sup>[38]</sup>,可能由于研究样本量不足、观察期过短,益生菌对微生物群落的影响有限,也可能与种植体周袋内解剖结构、环境与牙周袋环境存在一定差异,导致益生菌可能在此环境不能良好定植有关。但很多研究仍然对益生菌为种植体周围疾病的防治抱有期待,认为选择正确的菌种及菌株,经过长期试验可能为种植体周围疾病提供可选的治疗方法。

## 四、益生菌在其他口腔疾病防治中的应用

研究表明,使用含有益生菌的乳制品可以预防龋齿和促进脱矿的釉质再矿化<sup>[39]</sup>。服用含干酪乳杆菌的益生菌饮料可短期改善与龋病有关的微生物组成<sup>[40]</sup>。短期内每日摄入乳杆菌可显著降低唾液变形链球菌数量<sup>[41]</sup>,服用含有罗伊氏乳杆菌的益生菌含片可显著减少学龄期儿童龋齿相关细菌数量<sup>[42]</sup>。

真性口臭主要是由于口腔产生的挥发性硫化物引起的口腔异味,唾液链球菌M18可抑制口腔微生物产生挥发性硫化物和其他恶臭化合物产生<sup>[43]</sup>,可能成为治疗口腔异味的潜在手段。白念珠菌(*Candida albicans*)感染常见于佩戴义齿的老年人,乳酸乳杆菌(*Lactobacillus lactis*)、长双歧杆菌、干酪乳杆菌

和瑞士乳杆菌(*Lactobacillus helveticus*)对白念珠菌的生长有拮抗作用<sup>[44]</sup>。鼠李糖乳杆菌和动物双歧杆菌可能参与精神障碍相关口腔微生物群的调节作用<sup>[45]</sup>。目前也有研究指出,罗伊氏乳杆菌对阿弗他溃疡<sup>[46]</sup>和拔牙创愈合<sup>[47]</sup>无显著作用。

#### 五、益生菌在口腔疾病防治中的前景

益生菌在口腔生物医学领域前景广阔,将益生菌替代抗生素运用于牙周基础治疗后的辅助治疗,对儿童、老人、固定正畸、孕妇和外伤等不能维持良好口腔卫生措施的人群及难治性牙周疾病患者是更优的选择。目前,益生菌在口腔的应用还处于开发阶段,其远期疗效有待于进一步评估。

**利益冲突** 所有作者均声明不存在利益冲突

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