世界华人消化杂志 2013年10月8日; 21(28): 2981-2986
ISSN 1009-3079 (print) ISSN 2219-2859 (online)

文献综述 REVIEW

益生菌修复幽门螺杆菌相关黏膜屏障破坏的机制

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收稿日期: 2013-06-21 修回日期: 2013-07-11
接受日期: 2013-09-08 在线出版日期: 2013-10-08

Mechanisms underlying role of probiotics in recovering *Helicobacter pylori*-associated intestinal mucosal barrier damage

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Received: 2013-06-21 Revised: 2013-07-11
Accepted: 2013-09-08 Published online: 2013-10-08

Abstract

Helicobacter pylori (*H. pylori*) is closely associated with many gastrointestinal diseases, including peptic ulcers, chronic gastritis, gastric cancer and gastric mucosa-associated lymphoid tumors. In recent year, traditional triple therapy for *H. pylori* eradication has become less effective than the past, which is related to the resistance of bacteria. The addition of probiotics into the regimen has been proved to be able to significantly enhance the eradication rate and reduce side effects. Probiotics increase the eradication of *H. pylori* by recovering the damage of the chemical barrier, biological barrier, mechanical barrier and immune barrier.

Key Words: *Helicobacter pylori*; Probiotic; Intestinal mucosal barrier

Song Y, Cao XC, Yang YY, Jiang K. Mechanisms underlying role of probiotics in recovering *Helicobacter pylori*-associated intestinal mucosal barrier damage. Shijie Huaren Xiaohua Zazhi 2013; 21(28): 2981-2986 URL: http://www.wjgnet.com/1009-3079/21/2981.asp DOI: http://dx.doi.org/10.11569/wcjd.v21.i28.2986

■背景资料
幽门螺杆菌(*Helicobacter pylori*, *H. pylori*)感染会导致黏膜屏障损伤, 本文旨在归纳总结益生菌修复*H. pylori*引起黏膜屏障损伤的机制, 为益生菌在*H. pylori*治疗中的应用提供证据.

摘要

幽门螺杆菌(*Helicobacter pylori*, *H. pylori*)自发现至今被认为能够导致多种疾病的发生, 包括消化性溃疡、慢性胃炎、胃癌以及胃淋巴细胞相关性肿瘤. 近年来传统三联疗法(质子泵抑制剂+两种抗生素)对于*H. pylori*根除率明显下降, 这与细菌耐药性的增强有关. 在传统三联疗法基础上添加益生菌能够有效的提高*H. pylori*根除率, 同时降低不良反应的发生. 其机制可能为益生菌能够修复*H. pylori*引起的化学屏障、生物屏障、机械屏障以及免疫屏障的破坏, 恢复消化系正常防御功能, 从而辅助*H. pylori*根除. 此文将就益生菌修复*H. pylori*相关消化系屏障功能破坏的具体机制进行综述.

关键词: 幽门螺杆菌; 益生菌; 黏膜屏障

核心提示: 益生菌在幽门螺杆菌(*Helicobacter pylori*, *H. pylori*)相关疾病治疗中的应用逐渐引起了人们的重视. 益生菌能够修复*H. pylori*引起的黏膜屏障损伤, 恢复正常的消化系黏膜屏障功能, 从而有助于*H. pylori*相关疾病的治疗.

宋岩, 曹晓沧, 杨永妍, 姜葵. 益生菌修复幽门螺杆菌相关黏膜屏障破坏的机制. 世界华人消化杂志 2013; 21(28): 2981-2986
URL: http://www.wjgnet.com/1009-3079/21/2981.asp
DOI: http://dx.doi.org/10.11569/wcjd.v21.i28.2981

0 引言

幽门螺杆菌(*Helicobacter pylori*, *H. pylori*)是一种定植于胃黏膜的革兰氏阴性菌, 发展中国家

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益生菌的添加能够提高*H. pylori*的根除率，降低不良反应的发生.

约有79%-90%[1,2]的人群感染*H. pylori*, 发达国家感染率约为25%-50%[3]. *H. pylori*已被确认能够引起多种疾病, 主要包括消化性溃疡、慢性胃炎、胃癌以及胃淋巴细胞相关性肿瘤. 多年来, 人们一直都致力于研究如何将*H. pylori*根除. 目前, 传统的三联疗法(质子泵抑制剂+两种抗生素)为*H. pylori*的一线根除方案, 最初应用时效果理想, 但近年来, 三联疗法对于*H. pylori*的根除率有所下降, 这与抗生素滥用导致的*H. pylori*耐药性增强有着十分紧密的联系. 近年来多数实验证实, 在三联疗法根除*H. pylori*的同时, 对患者补充益生菌, 能够显著提高*H. pylori*根除率[4-8], 减轻不良反应[2,6,9-11]. 这引起越来越多的国内外学者开始关注消化系菌群与*H. pylori*之间的关系, 试图从一个新的角度重新思考*H. pylori*感染以及致病与消化系菌群之间关系, 从而为*H. pylori*的治疗开辟一条新的道路. 其中, 益生菌通过修复*H. pylori*引起的消化系黏膜屏障破坏, 辅助治疗*H. pylori*相关疾病成为了研究的新方向. 本文将就近年来的相关报道进行综述.

1 背景

消化系黏膜屏障主要由化学屏障、生物屏障、机械屏障以及免疫屏障构成, 他们共同维持消化系内稳态, 在预防致病菌感染中发挥着重要作用. 人在健康情况下消化系黏膜上皮表面覆盖含有离子、蛋白等物质的黏液屏障. 消化系内分布着种类丰富, 总量庞大[12]的菌群, 他们构成了消化系的生物屏障. 消化系黏膜上皮以及上皮间细胞连接作为机械屏障限制物质及微生物的通过. 而免疫细胞及炎性介质能够在致病菌入侵时及时激活并将其清除. 这些共同作用, 维持消化系内的稳态.

人类在出生后消化系内菌群开始定植, 消化系内菌群构成受多种因素的影响, 其中包括遗传学因素、饮食情况、环境暴露以及抗生素应用等[13]. 应用抗生素根除*H. pylori*会导致消化系内菌群失调, 引起诸多不良反应. 另外有研究表明, 抗生素灌胃后, 小鼠胃内原生菌群数量锐减, 胃内正常的微环境被破坏, 促进*H. pylori*的定植[14]. 益生菌是一类适当摄取后能够维持人体健康的微生物[15], 他们不仅大量定居于肠道内, 同时也是胃内原籍菌的一部分, 补充益生菌能够提高*H. pylori*的根除率, 降低三联疗法的不良反应. 由此我们重新思索: 长久以来, 我们一直着眼于*H. pylori*的致病以及治疗, 却忽视了*H. pylori*阳性患者在感染前是否存在消化系菌群失调、传统*H. pylori*根除治疗引起的菌群失调是否增加了*H. pylori*根治的难度. 因此, 应用益生菌恢复消化系菌群平衡, 修复消化系黏膜屏障, 治疗*H. pylori*相关疾病成为了一条可行的新思路.

2 益生菌修复*H. pylori*引起的化学屏障破坏

正常情况下, 胃内的pH值很低, 大约在1-4之间, 能够抑制*H. pylori*的活性. *H. pylori*产生尿素酶, 分解尿素产生二氧化碳和氨, 升高周围微环境的pH值, 从而起到自我保护作用. 益生菌能够产生有机酸, 如乳酸、乙酸等, 这些酸性物质能够降低胃内pH值, 破坏*H. pylori*建立的中性pH微环境[16], 降低尿素酶活性[17], 抑制*H. pylori*的生长. Celli等[18]的研究认为, 黏蛋白(mucin, MUC)在pH呈中性时为黏液状态, 在酸性条件下则为凝胶状态. 因此, 益生菌生成酸性物质, 降低pH值, 使得黏蛋白向凝胶状态转换, 阻碍了*H. pylori*的运动, 使其不易黏附于上皮组织而排出. 另外, 在大鼠模型胃损伤模型中, 双歧杆菌BF-1菌株能够提高Muc5ac的表达, 有助于增强黏膜的化学屏障作用[19]. 因此添加益生菌恢复正常的消化系化学屏障, 有助于黏液层*H. pylori*排出体外，从而提高*H. pylori*根除率.

3 益生菌修复*H. pylori*引起的生物屏障破坏

健康状态下, 由于胃内pH值较低, 常驻菌群数量相应的较少, 但其种类较丰富, 以厚壁菌门、放线菌门、变形菌门和拟杆菌门为主[20,21]. 胃内菌群的种类与比例和口腔内菌群相似[20,22], 这印证了胃内细菌主要来源为经口食入.

*H. pylori*感染对于胃内正常菌群的结构以及数量有所影响, 破坏了黏膜的生物屏障作用. 研究显示, 当*H. pylori*阳性时, 胃内细菌培养以*H. pylori*为主[23], 可达93%-97%, 厚壁菌门、放线菌门及拟杆菌门数量大幅降低, 非*H. pylori*变形菌、兼性厌氧菌数量有所上升, 胃内菌群多样性降低[20,24]. 除此之外，抗生素的应用对于消化系菌群也有着重要的影响. Hedvig等[25]对应用抗生素治疗胃部不适患者治疗前及治疗后口腔以及粪便内菌群的数量和种类进行分析, 发现抗生素的应用能够显著降低这两个位置的细菌多样性, 其中放线菌门数量明显降低, 且菌群状态恢复至治疗前水平所需时间最久达4年. 由此我们大胆猜测*H. pylori*感染后导致持续感染、溃疡、胃炎、胃癌的发生与*H. pylori*感染以及抗

生素使用所致胃内生物屏障破坏密切相关.

Mukai等[26]发现*L. reuteri*通过与*H. pylori*竞争上皮细胞表面中相同的糖基位点,使得*H. pylori*失去黏附位点而被排出体外. 有动物实验显示预先用乳酸杆菌和双歧杆菌灌胃能够有效地阻止小鼠胃内*H. pylori*的定植[14]. Lactobacillus johnsonii La1(LC1)能够有效抑制蒙古沙鼠胃黏膜上*H. pylori*的定植[27]. Myllyluoma等和Jensen等[28,29]关于多种益生菌在体外对于*H. pylori*抑制作用的实验得出结论, 乳酸杆菌、双歧杆菌以及丙酸杆菌的多个菌株能够有效的抑制*H. pylori*对Caco-2细胞的黏附. 这些结果证明了益生菌与*H. pylori*之间存在拮抗作用, 能够抑制*H. pylori*的黏附, 修复生物屏障的破坏.

4 益生菌修复*H. pylori*引起的机械屏障破坏

消化系上皮组织由上皮细胞及细胞间的上皮连接构成, 上皮连接分为紧密连接、黏合连接、桥粒和间隙连接. 益生菌能够修复紧密连接以及黏合连接, 使得*H. pylori*不易到达上皮深处, 从而提高抗生素的根除效果.

4.1 对紧密连接的修复 紧密连接由多种具有功能的蛋白组成, 包括连接黏附分子(junction adhesion molecule, JAM)-1、闭合蛋白、封闭蛋白、闭锁小带蛋白(zonula occlude, ZO)-1等, 这些蛋白能够防止物质自上皮间通过[30]. *H. pylori*感染后, 细胞毒素相关蛋白A(CagA)进入胃黏膜上皮细胞, 引起ZO-1从紧密连接移位至细菌附着部位[31-33]. 空泡毒素A(VacA)也能帮助松解紧密连接[34]. *H. pylori*产生的铵盐能够介导闭合蛋白的功能, 同时能够上调IL-1Ⅰ型受体的磷酸化[35], 破坏紧密连接[36]. 这些作用使得胃上皮紧密连接打开, 上皮通透性增加, *H. pylori*能够到达上皮更深处. 乳酸杆菌菌株WCFS1在人体内能够提高人胃黏膜ZO-1的水平和闭合蛋白的水平, 离体时能够促进ZO-1定位于紧密连接处, 提高黏膜屏障作用[37]. 尽管, 目前关于益生菌修复*H. pylori*引起的胃黏膜紧密连接损伤的报道并不多, 然而其修复其他原因引起的消化系屏障功能损伤的报道却十分丰富. 在炎症性肠病、感染性结肠炎、急性胃黏膜损伤等模型中, 益生菌能够防止ZO-1、闭合蛋白、封闭蛋白的丢失, 维持黏膜屏障功能[36,38,39]. 这些让我们有理由相信, 益生菌在修复*H. pylori*引起的胃黏膜上皮紧密连接破坏中, 有着可观的研究前景.

4.2 对黏合连接的修复 黏合连接中E钙蛋白是微生物黏附的主要受体. *H. pylori*分泌的产物能够引起编码E钙蛋白的*CDH1*基因甲基化, 以及E钙蛋白的细胞外域水解, 使得上皮细胞间的黏合连接松解, 这些都有利于*H. pylori*定植于胃黏膜, 引起病理性变化[40]. 研究表明, 在T84细胞屏障模型中, 乳酸杆菌能够调节编码E钙蛋白以及β钙蛋白基因的表达水平, 稳定黏膜屏障, 提高对致病菌的抵抗能力[41].

■创新盘点

近年来报道益生菌提高*H. pylori*根除率的文章日趋增多, 但关于益生菌这一作用的机制却众说纷纭. 本文旨在从修复黏膜屏障的角度为益生菌的在*H. pylori*相关疾病治疗中的应用提供证据.

5 益生菌修复*H. pylori*引起的免疫屏障破坏

致病菌进入消化系后可引起免疫系统恰当的激活, 消除致病菌. *H. pylori*感染后一方面可能引起免疫逃逸, 导致*H. pylori*持续感染. 另一方面会引起Smad7、核因子-κB(nuclear factor-κB, NF-κB)、肿瘤坏死因子-α(tumor necrosis factor-α, TNF-α)以及白介素-8(interleukin-8, IL-8)等细胞因子水平过度升高, 介导免疫反应, 引起胃黏膜上皮细胞的损伤. 益生菌能够平衡多种细胞因子的水平, 促进*H. pylori*的清除, 同时降低过度炎症反应. Wiese等[42]的研究表明与单纯*H. pylori*刺激相比, *H. pylori*和乳酸杆菌联合刺激能够提高INF-γ水平, 促进单核细胞MHC-Ⅱ(如HLA-DR)分子表达, 加强抗原呈递作用, 降低*H. pylori*免疫逃逸的发生, 从而有助于*H. pylori*的根除. 一项离体实验证明高剂量的嗜酸乳杆菌能够导致Smad7和NF-κB途径失活, 从而减轻*H. pylori*感染所引起的炎症反应[43-45]. 植物乳杆菌B7能够降低*H. pylori*感染大鼠血清TNF-α水平, 使多不饱和脂肪酸(polyunsaturated fat acids, PUFAs)的主要氧化产物丙二醛水平降低, 降低胃黏膜上皮细胞凋亡率, 以上作用与细菌数量正相关, pH = 4时较7时作用显著[46]. 含共轭亚油酸(由乳酸杆菌产生)的培养基能够抑制*H. pylori*引起的IL-8 mRNA以及TNF-α mRNA的升高, 在抗炎症反应以及抗癌变反应中起到了重要的作用[45]. 一项在儿童中进行的研究显示, 向*H. pylori*感染的儿童补充含有益生菌的酸奶, 患儿血清中IL-6水平有所下降, IgA和胃蛋白酶原水平有所上升, 这些都有助于抑制*H. pylori*在胃黏膜的定植[47], 恢复胃黏膜的免疫屏障作用，提高根除效果.

6 结论

正常情况下, 消化系具有屏障作用, 对于致病菌有着一定的防御功能. 消化系内寄居着大量的微生物, 不同部位的菌群构成差别较大. 胃内由于特殊的低pH环境, 微生物数量相对较少, 但

■应用要点
本文为益生菌在治疗*H. pylori*相关疾病的临床应用提供有力的证据.

菌群种类丰富. Linz等[4]认为*H. pylori*在50000年前就开始寄居于人体内, 并随人类共同进化. *H. pylori*可导致胃部多种疾病的发生, 一直被认为是一种致病菌, 因此一直致力于通过了解*H. pylori*的生物学特性来提高*H. pylori*的根除率, 从而治疗*H. pylori*所引起的相关疾病. 然而, 随着传统三联疗法对于*H. pylori*根除率的下降, 以及不良反应的增多, 探索新的治疗方案成为了一项紧迫的任务. 是否能够通过添加益生菌来恢复胃黏膜屏障功能, 阻断*H. pylori*所引起的病理变化, 并辅助根除*H. pylori*. 本文通过总结近年来有关益生菌治疗*H. pylori*的研究, 得出初步结论: 益生菌能够稳定胃黏膜屏障, 修复*H. pylori*引起的黏膜屏障破坏, 在三联疗法的基础上加入益生菌有助于*H. pylori*的根除. 然而关于益生菌菌株的选择、剂量、给予时间等具体问题尚无定论[48]. 关于*H. pylori*与消化系内菌群的关系以及*H. pylori*相关疾病的治疗仍然存在极大的盲区需要我们去探索.

7 参考文献

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■同行评价

提高幽门螺杆根除率是目前临床研究的热点, 本文从益生菌角度出发, 选题具有一定新意.

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编辑 田滢 电编 鲁亚静

ISSN 1009-3079 (print) ISSN 2219-2859 (online) DOI: 10.11569

• 消息 •

《世界华人消化杂志》于 2012-12-26 获得 RCCSE 中国权威学术期刊 (A+) 称号

本刊讯 《世界华人消化杂志》在第三届中国学术期刊评价中被武汉大学中国科学评价研究中心(RCCSE)评为“RCCSE中国权威学术期刊(A+)”. 本次共有6 448种中文学术期刊参与评价, 计算出各刊的最终得分, 并将期刊最终得分按照从高到低依次排列, 按照期刊在学科领域中的得分划分到A+、A、A-、B+、B、C级6个排名等级范围. 其中A+(权威期刊)取前5%; A(核心期刊)取前5%-20%; A-(扩展核心期刊)取前20%-30%; B+(准核心期刊)取前30%-50%; B(一般期刊)取前50%-80%; C(较差期刊)为80%-100%.