

益生菌和胃肠道疾病

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收稿日期: 2011-04-19 修回日期: 2011-05-23

接受日期: 2011-06-02 在线出版日期: 2011-06-18

Probiotics and gastrointestinal diseases

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Received: 2011-04-19 Revised: 2011-05-23

Accepted: 2011-06-02 Published online: 2011-06-18

Abstract

The intestinal microbiota plays a key role in maintaining the normal function of the human gastrointestinal tract. Many probiotics are derived from human gut flora, and have been confirmed to be valuable in the management of gastrointestinal diseases. Probiotic effects are strain-specific, they do not act through the same mechanisms, and nor are all probiotics good for health. Nevertheless, they do have several common characters in that they exert anti-inflammatory effects, they employ different strategies to antagonize competing microorganisms, and they induce cytoprotective changes in the host either through enhancement of barrier function, or through up-regulation of the expression of cytoprotective host proteins. In this review we focus on several probiotics: a Gram-negative probiotic (*Escherichia coli* Nissle1917), a Gram-positive probiotic bacterium (*Lactobacillus Rhamnosus* GG, LGG), a bacterial mixture (VSL#3), and a yeast probiotic (*Saccharomyces boulardii*).

Key Words: Probiotics; Intestinal microbiota; In-

flammation; Colitis

Jiang Y, Liu J, Ren HY. Probiotics and gastrointestinal diseases. *Shijie Huaren Xiaohua Zazhi* 2011; 19(17): 1813-1818

摘要

在人类的胃肠道功能中, 肠道微生物发挥了重要的作用。很多益生菌是从原有的肠道细菌中发现出来的, 并被证实对一些胃肠道疾病具有临床功效。益生菌的作用具有菌株特异性, 既不是通过共同的机制发挥作用, 也不是所有的益生菌都有益于健康。在抗炎作用上, 他们有几种共同的功能, 如通过不同的方式和其他微生物竞争拮抗, 通过增强宿主细胞的防御功能或是正调节宿主细胞保护蛋白的表达, 从而激发宿主细胞的保护功能。本文选择介绍一些益生菌: 革兰氏阴性益生菌如尼氏大肠杆菌 (*Escherichia coli* Nissle 1917), 革兰氏阳性益生菌如鼠李糖乳杆菌 (*Lactobacillus rhamnosus* GG, LGG), 细菌混合物 (VSL#3) 和一种酵母益生菌如鲍氏酵母菌 (*Saccharomyces boulardii*)。

关键词: 益生菌; 肠道微生物; 感染; 结肠炎

蒋焱, 刘俊, 任宏宇. 益生菌和胃肠道疾病. 世界华人消化杂志 2011; 19(17): 1813-1818

<http://www.wjgnet.com/1009-3079/19/1813.asp>

0 引言

细菌是人体正常功能的重要组成部分。多数益生菌都从人体内众多的共生细菌中分离出来。这些微生物在人体的新陈代谢和营养吸收中, 发挥了关键的作用。他们可以合成一些化合物如K和B族维生素; 分解胆固醇; 合成短链脂肪酸, 如丁酸盐类; 分解在人体内不能被吸收的多糖从而减少一些能量损失^[1]。通过激发免疫系统中的树突状细胞, 增强宿主的免疫防御功能^[2], 并与病原菌竞争结合肠道上皮细胞, 而达到抑制病原菌的作用^[3]。此外, 他们也产生一些细菌性产物, 例如被称作细菌素的小分子肽类, 杀灭其他的病原微生物^[4]。人体的共生菌可以通过与一

■背景资料

人类体内细菌的数目远多于细胞数目, 胃肠道细菌的数目范围为 10^{12} 数量级。这些微生物在人体的新陈代谢, 营养吸收, 宿主的免疫以及胃肠道的防御功能中都起到了不可或缺的作用。因此有人称益生菌为被遗忘的器官。益生菌的种类繁多, 无论是在科学研究、医疗应用以及人们的日常生活中, 益生菌都是一个热门话题。

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■ 研究前沿

益生菌和宿主肠道之间的免疫关系是近年来研究的热点。益生菌和宿主的免疫系统之间的相互关系复杂。一些胃肠道疾病如炎症性肠病、肠易激综合征的发病机制与肠道菌群失调有关,因此在临床上使用益生菌治疗胃肠道疾病也是近年来研究的重点。但是益生菌种类繁多,他们作用具有种株特异性,不是通过共同的机制发挥作用。

些病原菌竞争营养,而起到防御功能。总之,人体与共栖细菌和谐共处,人体给共栖细菌提供营养和住所,作为回报,他们对人体的新陈代谢和营养吸收起到很重要的作用,还可以防止病原菌的侵害。

益生菌的作用具有种株特异性,他们并不是通过同等的机制起作用,也不是所有的益生菌都有保健的功效。这篇文章难以全面介绍所有益生菌,将选择性重点介绍一些益生菌。

1 尼氏大肠杆菌1917

尼氏大肠杆菌1917(*E.coli* Nissle 1917)与其他益生菌不同,他是一种革兰氏阴性细菌,而大多数益生菌都是革兰氏阳性细菌。在常规抗生素应用之前,这个菌株已经在市场上用于治疗腹泻接近100年^[5]。

1.1 基础实验 和其他致性病的大肠杆菌菌株不同,益生菌*E.coli* Nissle 1917缺乏与他同种的病原菌株中普遍存在的致病因子。相反,他却具有几种“适应因子”,使他与其他大肠杆菌种中致病或非致病菌种相比具有生存优势^[5]。在大肠黏膜上,*E.coli* Nissle 1917具有抗炎和细胞保护功能,但是他发挥抗炎效应的机制还未清楚。一个采用葡聚糖硫酸钠(dextran sodium sulfate, DSS)诱导的结肠炎模型实验中,试图明确Nissle对结肠炎症的保护作用是否由TLR介导。以含有Nissle的盐水作为对照来喂养野生型、TLR-2缺乏和TLR-4缺乏的小鼠,评估动物的疾病活动性、黏膜损害情况和细胞因子的分泌。在野生型的小鼠中,*E.coli* Nissle 1917增加了结肠炎评分,降低了肿瘤坏死因子 α (tumor necrosis factor alpha, TNF- α)和单核细胞趋化蛋白-1(monocyte chemoattractant protein-1, MCP-1)的分泌,但是没有增加疾病活动指数(disease activity index, DAI)的评分。在Toll样受体(Toll-like receptor, TLR)2和TLR-4基因敲除老鼠,观察到镜下炎症或中性粒细胞的聚集^[6],表明*E.coli* Nissle 1917的抗炎机制可能通过由核因子 κ B(nuclear factor kappa B, NF- κ B)介导的依赖TLR-2-TLR-4的途径产生。然而,另一个在人肠道上皮细胞HCT15的研究表明*E.coli* Nissle 1917抑制TNF- α 介导的白介素-8(interleukin-8, IL-8)表达,但他不影响NF- κ B的活性、核易位或是DNA连接^[7]。*E.coli* Nissle 1917发挥抗炎效应的机制仍有待研究。

另一研究证实,*E.coli* Nissle 1917可以增强人类 β -防御素的表达^[8]。防御素是一种由肠道产

生的抗菌肽,能保护和防御病原菌对宿主的入侵。炎症性肠病和防御素低表达水平是相关的^[9],因此*E.coli* Nissle 1917可通过防御素的机制来提供保护,如限制一些有害细菌对肠道上皮细胞的黏附作用。

1.2 临床研究 一些临床研究表明在维持溃疡性结肠炎的缓解治疗中,*E.coli* Nissle 1917具有与金标准美沙拉秦同样的功效^[5,10-12]。1997年,120例静止期溃疡性结肠炎患者的双盲试验研究,口服美沙拉秦或是大肠杆菌制剂12 wk后,对比他们病情的复发率、无复发维持时间和总体评估。美沙拉秦组的复发率为11.3%,而*E.coli* Nissle组为16.0%,同时美沙拉秦组的无复发维持时间为103 d \pm 4 d,而*E.coli* Nissle组的无复发维持时间为106 d \pm 5 d。两组的总体评估和耐受性是相同的^[10]。接下来进行了一个更大的临床双盲试验,327例溃疡性结肠炎缓解期的患者,随机接受美沙拉秦或是*E.coli* Nissle 1917治疗12 mo后,用内镜和组织学活动指标来评估结果。通过“每份治疗协议”来分析复发率,*E.coli* Nissle组复发率为40/110(36.4%)而美沙拉秦组的复发率为38/112(33.9%)($P = 0.003$)。用“意向治疗”分析,包括没严格按照协议但是每天至少服用1次研究药物的患者,*E.coli* Nissle组的复发率是45.1%,而美沙拉秦组的复发率是37.0%($P = 0.013$)。试验中没有严重不良事件被报道^[11]。*E.coli* Nissle 1917用于治疗肠易激综合征同样具有临床功效^[13]。

2 鼠李糖乳杆菌

乳酸杆菌是最普遍被用作益生菌的一种细菌。他们用于食物和乳品工业历史悠久,鼠李糖乳杆菌(*Lactobacillus rhamnosus* GG, LGG)是被Sherwood Gorbach和Barry Goldwin发现的。他们从健康的志愿者粪便样本中分离出来,可以耐受胆汁和胃酸^[14]。

2.1 基础实验 LGG可以增强宿主细胞的防御功能^[15]。在一个对患有轻至中度活动性克罗恩病的儿童的研究中,通过甘露醇/纤维二糖的通透性测试,发现接受LGG治疗会改善肠道的通透性,在接受益生菌治疗12 wk后达到最大效果^[16]。2 wk大的大鼠用牛奶、加有LGG的牛奶或水饲养后,用尤斯(using)灌流室分析他们肠道的通透性。在乳鼠上,发现LGG可以防止由牛奶导致的肠道通透性增加。在体外,LGG对上皮细胞预处理可以保护屏障功能免受肠道病原菌血清型

O157:H7的肠道出血性大肠杆菌(enterohemorrhagic *E.coli*, EHEC)侵害^[17]. 在这个实验中, 细胞接受LGG预处理, 感染*E.coli* O157:H7后, 用电子显微镜检查细胞. 尽管不能阻止胞质空泡的形成, 但他可以保护细胞结构的完整, 尤其是防止由*E.coli* O157:H7造成的紧密连接的破坏. 通过检测跨膜电阻, 进一步发现LGG预处理后可以部分阻止由*E.coli* O157:H7介导的人肠道上皮细胞T84屏障功能的丧失. LGG起作用的另一潜在机制包括诱导热休克蛋白(heat shock protein, HSP)的表达^[18]. 在肠道上皮细胞上LGG合成和分泌的小分子复合物诱导一种时间浓度依赖性的HSP25和HSP72的表达, 并且发现HSP72可以稳定和阻止细胞蛋白质的变性, 保护肠道上皮细胞免受氧化剂介导的损害^[19]. 在体外LGG分泌的2种蛋白质P40和P70可以减轻过氧化氢对肠道上皮的氧化伤害作用^[20]. 除此之外, 他们在阻止细胞因子诱导的人和老鼠上皮细胞的凋亡过程中起作用^[21]. 总之, 这些体内和体外研究都提供了LGG保护肠道屏障功能的证据.

2.2 临床研究 几个临床试验已经将LGG用于治疗腹泻, 他被成功地用于治疗儿童的急性腹泻^[22-25]. LGG治疗轮状病毒腹泻最有效, 在LGG处理组的患者中, 他可以缩短病程和减少腹泻的频率^[26,27]. 他在治疗医源性和抗生素相关性腹泻(antibiotic associated diarrhea, AAD)上也有效^[28,29]. 一个检测益生菌对AAD作用的Meta分析, 包括总数6个使用LGG的试验, 这些试验患者总数达817例. 计算加权比率, 得出防治1例不良事件的发生需治疗的总病例数(number need to treat, NNT)为6^[30,31], 即防止一个患者AAD的病情进展, 需要以LGG治疗6个接受抗菌素的患者.

3 益生菌VSL#3

益生菌VSL#3是由8种不同革兰氏阳性细菌组成的混合菌群, 他们是嗜热性唾液链球菌亚种(*Streptococcus salivarius subsp.thermophilus*)、干酪乳杆菌(*Lactobacillus casei*)、植物乳杆菌(*Lactobacillus plantarum*)、嗜酸乳杆菌(*Lactobacillus acidophilus*)、保加利亚德氏乳杆菌(*Lactobacillus delbrueckii subsp.bulgaricus*)、长双歧杆菌(*Bifidobacteria longum*)、幼儿双歧杆菌(*Bifidobacteria infantis*)和短双歧杆菌(*Bifidobacteria breve*).

3.1 基础实验 对VSL#3的研究发现他们分泌的产物抑制关键炎症转录因子NF- κ B, 并且通过封闭

肠道上皮细胞蛋白酶的活性来抑制NF- κ B抑制因子(inhibitor of NF-kappa B, I κ B)的降解^[32]. 此外, VSL#3的产物还能诱导HSP的表达, 这可以避免细胞受氧化剂的伤害. 通过激活转录因子热休克因子-1(heat shock factor-1, HSF-1)来诱导HSP表达. VSL#3活菌体及其分泌的细菌素都可以通过剂量依赖性的方式来诱导HSP在肠道上皮细胞上的表达^[32]. 在2种不同的实验性结肠炎模型中, 测试了VSL#3细菌分离DNA的抗炎活性^[33,34]. 第1个实验, 用从VSL#3菌群中分离出DNA喂养IL-10缺乏的老鼠, 2 wk后分析其取出的结肠. 结果表明, 接受VSL#3DNA喂养的动物与对照组相比, 组织学损伤更少, 以及出现了TNF- α 的降低^[33]; 第2个实验, 采用DSS处理的实验性结肠炎模型, 在动物暴露于DSS前10 d, 动物先接受DNA酶, 然后接受VSL#3的DNA, 或是大肠杆菌的DNA预处理, 再以DSS处理7 d. 结果发现接受VSL#3益生菌DNA和*E.coli* DNA的DSS结肠炎模型, 后一组的结肠炎更严重. 进一步用TLR9缺乏的小鼠实验, 研究者认为TLR9信号肽在介导抗炎效应中起着必要的作用^[34]. VSL#3可以通过下调 β -防御素2的表达治疗小鼠结肠炎^[35].

3.2 临床研究 在一个开放性试验中, 为了明确VSL#3治疗活动性溃疡性结肠炎患者的价值, 这些轻至中度($n = 34$)溃疡性结肠炎的患者, 接受混合益生菌治疗6 mo后再次评估. 采用目的治疗分析, 在VSL#3治疗的患者中有53%的缓解率, 9%的患者没有变化, 9%患者症状加重, 5%的患者未完成最终评估^[36]. 该研究的有趣环节是在活检组织中用16S rRNA的核酸标记序列来测定VSL#3菌种的表型. 在一个随机、双盲试验中, 144例轻至中度溃疡性结肠炎患者已经接受至少4 wk 5-氨基水杨酸治疗(美沙拉秦1.6 g/d或巴柳氮4.5/d), 或是接受免疫抑制剂[硫唑嘌呤1.5 mg/(d \cdot kg)或是6-巯嘌呤1 mg/(d \cdot kg)]治疗, 病情依旧复发. 实验组(71例)加用VSL#3 3.6×10^{11} CFU/d. 对照组(73例)服用安慰剂. 研究持续8 wk后VSL#3组溃疡性结肠炎DAI下降50%的患者明显多于对照组($P = 0.031$)^[37]. VSL#3菌群对慢性憩室炎^[38], 及溃疡性结肠炎患者因急性肠炎起病行结肠切除、回肠储袋肛管吻合术后维持治疗均有临床功效^[39].

4 鲍氏酵母菌

鲍氏酵母菌(*Saccharomyces boulardii*), 是少数不

■ 相关报道

一个检测益生菌对AAD作用的Meta分析, 包括总数6个使用LGG的试验, 这些试验患者总数达817例. 计算加权比率, 得出防治1例不良事件的发生需治疗的总病例数(NNT)为6, 即防止一个患者AAD的病情进展, 需要以LGG治疗6个接受抗菌素的患者.

同行评价

本文选题新颖, 条理清晰, 有较好的可读性.

是细菌来源, 被普遍作为益生菌的微生物之一. *S. boulardii* 是酿酒酵母菌的一个亚株, 他的最适生长温度是37 °C, 并且能通过所有胃肠道存活, 他并不在结肠上长期定殖^[40,41].

4.1 基础实验 *S. boulardii* 可以黏附在上皮细胞的细胞壁, 通过胃肠道, 产生一种蛋白酶, 可以裂解难辨梭状芽孢杆菌毒素A和B^[42,43]. *S. boulardii* 可以刺激IgA的分泌并且诱导对难辨梭状芽孢杆菌毒素A特异性IgA的免疫应答^[44,45]. 研究表明IgA具有抗毒素作用^[46], 因此*S. boulardii* 在治疗难辨梭状芽孢杆菌相关性疾病(*Clostridium difficile* associated disease, CDAD)上有着重要意义. 一个实验表明*S. boulardii* 可能合成和分泌另一种有待确定的物质, 他可以保护肠道上皮细胞免受伤害. 从*S. boulardii* 培养物中提取热灭活的培养液, 可以在体外保护上皮细胞, 免受难辨梭状芽孢杆菌毒素A对其防御功能的破坏. 肠道上皮细胞Caco-2种植在Transwell型培养皿中, 加入难辨梭状芽孢杆菌毒素A前, 加入热灭活的*S. boulardii* 条件培养基(conditioned media, CM)进行过夜预处理. 在加入毒物的1 h前和加入毒物后120 min, 每30 min用电位仪的电极测试细胞的跨膜电极的变化. 经过*S. boulardii* CM预处理的细胞与对照组相比细胞防御功能丧失的更少^[47].

4.2 临床研究 CDAD是由难辨梭状芽孢杆菌(*Clostridium difficile*)造成的. 当病情严重时, CDAD会导致结肠炎, 威胁生命导致死亡. 很多患CDAD接受治疗的患者, 都会经历疾病的多次复发, 并且不能完全清除他的感染. 几个研究已经证实^[32,41,48-50], *S. boulardii* 具有改善AAD和根除复发性CDAD临床的作用. *S. boulardii* 已经被证实, 降低CDAD复发率, 尤其是治疗时, 联合使用大剂量的万古霉素, 可使CDAD的复发率降低至50%^[51]. 使用这种活酵母菌作为益生菌, 必须要谨慎^[52-54]. 一个关于在医院爆发的*S. boulardii* 血流感染的报道, 发现*S. boulardii* 有关的真菌血症发生在未接受*S. boulardii* 治疗的患者身上^[52].

5 结论

当前的资料表明了益生菌可用于一些临床疾病, 例如*E. coli* Nissle 1917用于溃疡性结肠炎维持治疗, LGG和*L. reuteri* 治疗轮状病毒腹泻^[55], VSL#3治疗储袋炎, *S. boulardii* 治疗难辨梭状芽孢杆菌, LGG和*S. boulardii* 治疗AAD等. 除了在临床作用和成分不同外, 益生菌他们作用的机制各不相同. 多数细菌都有细胞保护作用(诱导HSP和黏

蛋白的表达)和抗炎作用(通常是通过不同的步骤而作用于共同的NF- κ B活化通路). 然而益生菌并不总是有益的^[54,56-60]. 益生菌可能导致感染, 尤其是在留置静脉导管的患者上益生菌的使用增加了侵入性感染的风险^[53,57]. 益生菌对胰腺炎的临床功效有待进一步研究^[61,62]. 一个测试益生菌对胰腺炎功效的临床试验, 试验被迫很早就终止, 由于益生菌组病情进展的更坏. 在益生菌组有24例死亡, 而对照组有9例, 益生菌组报道有9例肠缺血坏死, 在对照组却没有^[61]. 这个试验的结果给我们一个很好的启示, 我们仍然没有完全了解益生菌复杂的作用机制, 迫切需要更好的明确其机制的科学原理^[63,64]. 通过对人类微生物的研究, 更好的理解宿主与细菌的相互关系^[65-67].

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编辑 曹丽鸥 电编 何基才