微生物学报
Acta Microbiologica Sinica
2024, 64(7): 2224–2241
http://journals.im.ac.cn/actamicrocn
DOI: 10.13343/j.cnki.wsxb.20230802

Review 综 述

儿童肠道菌群与食物过敏关系的研究进展

杨善平[1]，赵童[2]，余辉艳[2]，周催[2*]

1 首都医科大学基础医学院，北京 100069
2 首都医科大学公共卫生学院，北京 100069

杨善平, 赵童, 余辉艳, 周催. 儿童肠道菌群与食物过敏关系的研究进展[J]. 微生物学报, 2024, 64(7): 2224-2241.
YANG Shanping, ZHAO Tong, YU Huiyan, ZHOU Cui. Research progress in the relationship between gut microbiota and food allergy in children[J]. Acta Microbiologica Sinica, 2024, 64(7): 2224-2241.

摘　要：食物过敏(food allergy, FA)在儿童中的发生率逐年升高，严重影响其生活质量，已经成为全球面临的公共卫生问题之一。近年来，人们发现 FA 儿童的肠道菌群组成与健康儿童有显著差异。深入研究发现，肠道菌群可通过调节树突状细胞、辅助性 T 细胞、调节性 T 细胞、肥大细胞和粒细胞等免疫细胞维持免疫平衡，也可通过多种方式增强肠道屏障功能，抑制 FA 的发生。在已有研究基础上，益生菌和益生元在治疗儿童 FA 方面也得到了一定应用，但目前的应用效果并不明确。本文以婴幼儿 FA 在全球范围内患者规模日益扩大为背景，综述了肠道菌群影响 FA 的部分机制，总结了近年部分益生菌和益生元在治疗和预防婴幼儿 FA 方面的应用，并为肠道菌群在FA发生和发展中的作用机制研究和益生菌及其相关代谢产物在儿童FA治疗和预防中的应用提出了新思路，对促进婴幼儿 FA 治疗方法和策略的研究有重要意义。

关键词：食物过敏；儿童；肠道菌群；益生菌

资助项目：国家自然科学基金(82273633)
This work was supported by the National Natural Science Foundation of China (82273633).
*Corresponding author. E-mail: zhoucui@ccmu.edu.cn
Received: 2023-12-27; Accepted: 2024-03-25; Published online: 2024-03-28

Research progress in the relationship between gut microbiota and food allergy in children

YANG Shanping[1], ZHAO Tong[2], YU Huiyan[2], ZHOU Cui[2*]

1 School of Basic Medical Sciences, Capital Medical University, Beijing 100069, China
2 School of Public Health, Capital Medical University, Beijing 100069, China

Abstract: Food allergy (FA) with growing incidence has emerged as one of the public health problems around the world as it seriously affects the life quality of children. Recent studies have discovered that there are significant differences in the composition of gut microbiota between the children with FA and healthy children. In-depth studies have reported that gut microbiota can help to maintain immune balance by regulating immune cells such as dendritic cells, helper T cells, regulatory T cells, mastocytes, and granulocytes. In addition, gut microbiota can enhance the intestinal barrier function to inhibit FA in a variety of ways. On the basis of research results from animal experiments, probiotics and prebiotics have been used in the treatment of FA in children, whereas the effect is not ideal. As FA occurs in a growing number of children in the world, this article reviews some mechanisms of gut microbiota in influencing FA and summarizes the application of probiotics and prebiotics in the treatment and prevention of FA in children in recent years. Furthermore, this article proposes new ideas for deciphering the mechanism of gut microbiota in regulating FA and applying probiotics and probiotic metabolites in the treatment and prevention of FA in children, which is of great significance for promoting the research on the treatment of FA in children.

Keywords: food allergy; children; gut microbiota; probiotics

食物过敏(food allergy, FA)是指机体暴露于某种特定食物时出现的由特异免疫反应引起的不良健康影响[1], 美国国家过敏症和传染病研究所(National Institute of Allergy and Infectious Diseases, NIAID)将其定义为“暴露于特定食物后可重复发生的免疫不良反应”[2]，可由免疫球蛋白(immune globulin, Ig) E、非 IgE 和混合机制介导产生[1], 常见的 FA 是由 IgE 介导的I型超敏反应。FA 患儿常表现出皮肤症状(如风团、弥漫性瘙痒、面部潮红等)、胃肠道症状(如口腔瘙痒、恶心、呕吐等)、呼吸道症状(如打喷嚏、鼻漏、充血、呼吸困难、胸闷、咳嗽等)和循环系统症状(如心动过速、低血压、头晕等)等全身症状[1]，其中皮肤症状最为典型[3]，严重者可能发生休克，危及生命[1]。FA 已经成为全球多国儿童中的常见疾病，而且 FA 在儿童中的发病率呈上升趋势[1,3]。流行病学调查显示，美国儿童 FA 患病率为 5.8%[4]。在荷兰的 10 岁儿童中，被医生确诊的 FA 患儿占 2.3%[5]。流行病学调查发现，我国江西省 6−11 岁儿童自我报告的 FA 患病率为 6.15%[6]。Meta 分析结果显示，在中国 4−17 岁的儿童中，FA 患病率为 10%，婴儿患病率为 6%[7]。在引起 FA 的食物中，鸡蛋过敏和牛奶过敏在 5 岁以下儿童中最为常见[8]，而在 5 岁以上儿

童中，引起 FA 的食物还包括花生、坚果和海鲜(贝类)[9-10]。一项北京地区针对 0−14 岁儿童开展的研究也发现，牛奶和鸡蛋过敏主要发生在婴儿期，水果过敏主要发生在学龄前和学龄儿童中[3]。由此可见，尽管不同国家和地区的儿童 FA 患病率和过敏性食物具有一定差异，但 FA 已经成为全球多国儿童共同面临的公共卫生问题之一。

关于婴幼儿 FA 发生的原因有许多说法，包括“卫生假说”、双重屏障假说、维生素 D 缺乏等，其中“卫生假说”受到了广泛的关注[11]。“卫生假说”认为人类过敏性疾病患病率不断上升是因为环境卫生程度不断改善，人们所接触到的微生物日益减少[12]。研究发现，生命早期暴露于较差卫生环境中的人群过敏性疾病发生率显著低于微生物暴露较少的人群[13]，这提示微生物在过敏性疾病中发挥重要作用。微生物广泛分布于人体的皮肤、呼吸道和肠道中，儿童肠道菌群的最初来源与其分娩方式相关，阴道分娩婴儿的肠道微生物群来自母体的阴道和肠道微生物群[14]，剖宫产婴儿的肠道微生物来自皮肤微生物群[15]。随着儿童的生长发育，其肠道微生物群会更多受到环境因素的影响，包括膳食因素和生活环境等。

近年来，许多研究发现 FA 患儿的肠道菌群结构与健康儿童有显著差异，一些肠道菌群在健康儿童中的丰度显著高于 FA 患儿[4,16-21]，在分析现有 FA 与肠道菌群关系文献的基础上，本文整理出与儿童 FA 关系密切的有益肠道菌群，并对其进行了生物学分类(图 1)。同时，我们还从肠道菌群调节免疫细胞和维持肠道屏障功能方面总结了肠道菌群影响儿童 FA 的相关机制，为儿童 FA 的预防或缓解提供一定的科学依据和理论基础。

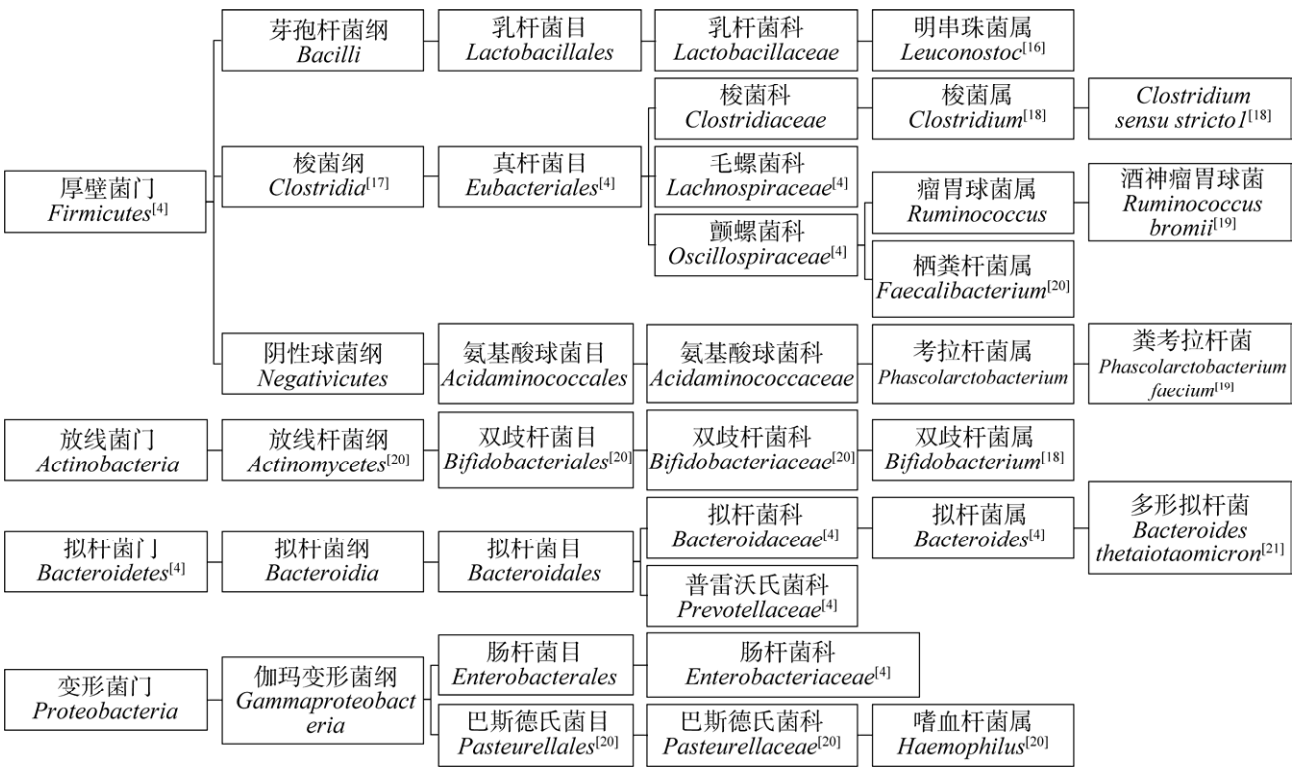

图 1　与儿童食物过敏关系密切的有益肠道菌群

Figure 1　Beneficial gut microbiota closely correlate with food allergies in children.

1 肠道菌群影响儿童食物过敏的机制

1.1 肠道菌群通过调节免疫细胞维持免疫平衡

FA 的发生过程可分为致敏阶段和效应阶段，2 个阶段均需要各类免疫细胞的参与。研究者们发现，在 FA 的发生或调节过程中，树突状细胞(dendritic cells, DCs)、辅助性 T 细胞(helper T cells, Th)、调节性 T 细胞(T regulatory cell, Treg)、B 细胞、肥大细胞和粒细胞等免疫细胞均发挥了重要作用，肠道菌群可通过调节免疫细胞抑制或缓解 FA 的发生，以此维持人体免疫平衡[22]。肠道菌群主要通过其代谢产物短链脂肪酸(short-chain fatty acid, SCFA)影响免疫细胞，SCFA 是结肠中最丰富的微生物代谢物[23]，丁酸盐和丙酸盐是 SCFA 中发挥健康促进功能的主要成分[24]。SCFA 能通过激活 G 蛋白偶联受体、影响组蛋白去乙酰化酶或改变细胞内代谢等方式作用于免疫细胞、维持免疫稳态[25]，以调节 FA 的发生。

1.1.1 树突状细胞

DCs 是一种重要的抗原呈递细胞(antigen presenting cell, APC)，能将食物抗原加工后呈递给 T 细胞，从而引发免疫反应。DCs 在调节 $CD4^+$ 初始 T 细胞的增殖和分化中起主要作用，其中 $CD11c^+CD103^+$DCs 对 Treg 的活化和增殖有重要作用[26]，而成熟的 $CD11^+$DCs 是一种重要的 APC，在 $CD80^+$DCs 或 $CD86^+$DCs 的共刺激下可促进I型辅助性 T 细胞(type I helper T cells, Th1)与II型辅助性 T 细胞(type II helper T cells, Th2)的激活与分化，进而调节机体 FA 的发生。因此，提高机体内 $CD11c^+CD103^+$DCs 水平、降低机体内 $CD80^+$DCs 或 $CD86^+$DCs 水平能抑制 FA 的发生。本课题组 Zhou 等[27]的研究结果显示口服卵清蛋白(ovalbumin, OVA)能诱导小鼠 FA 并导致其肠道菌群紊乱，同时 FA 小鼠肠系膜淋巴结(mesenteric lymph nodes, MLN)和脾中 $CD11c^+CD103^+$DCs 水平显著下降，$MHCII^+CD86^+$DCs 和 $CD103^+CD86^+$DCs 水平显著升高；相关性分析发现，FA 小鼠粪便中 *Mollicutes*_RF39 目、梭菌纲(*Clostridia*)、柔膜体纲(*Mollicutes*)、厚壁菌门(*Firmicutes*)和柔壁菌门(*Tenericutes*)中部分菌属的丰度与 MLN 中 $CD11c^+CD103^+$DCs 水平呈正相关，与 $MHCII^+CD86^+$DCs 或 $CD103^+CD86^+$DCs 水平呈负相关，这说明肠道菌群可能通过调节 DCs 影响机体免疫反应的发生。Tian 等[28]研究发现，口服动物双歧杆菌(*Bifidobacterium animalis*) KV9 和阴道乳杆菌(*Lactobacillus vaginalis*) FN3 可抑制 FA 小鼠白细胞介素(interleukin, IL)-4 和 IL-12 相关基因的表达，显著降低 FA 小鼠肠道 $CD11c^+MHCII^+$DCs、$CD11c^+CD80^+$DCs 和 $CD11c^+CD86^+$DCs 在 $CD11c^+$DCs 中的占比，降低小鼠肠道相关免疫组织中成熟 DC 的水平，从而减少参与抗原呈递的 DCs 并抑制 Th2 免疫反应的发生。Fu 等[29]的研究结果表明，口服干酪乳杆菌(*Lactobacillus casei*) Zhang 可通过促进 *Aldh1a2* 和 *Ido* 基因的表达，显著增加 FA 小鼠脾脏 $MHCII^+$细胞中 $CD11c^+CD103^+$DCs 的水平，进而促进机体免疫耐受的形成。

1.1.2 辅助性 T 细胞

Th 的分化情况可以反映机体免疫系统所处的状态。正常免疫状态下，机体免疫系统中的 Th1 与 Th2 的水平处于平衡状态，当 Th2 被大量激活时，会释放大量 IL-4、IL-5 等细胞因子，

促进 B 细胞的增殖并产生免疫球蛋白，使机体处于致敏状态，导致过敏反应的发生。Chen 等[30]研究发现，鼠李糖乳杆菌(*Lactobacillus rhamnosus*) GG 可调节脾脏中的 T 细胞受体(T cell receptor, TCR)信号通路，升高干扰素(interferon, IFN)-γ mRNA 的水平，降低 IL-4 mRNA、IL-13 mRNA 和转化生长因子(transforming growth factor, TGF)-β mRNA 水平，维持 Th1/Th2 平衡，从而减轻 β-伴大豆球蛋白(β-conglycinin)过敏小鼠的过敏反应。Lu 等[31]研究发现，植物乳植杆菌(*Lactiplantibacillus plantarum*) CCFM1189、罗伊特氏黏液乳杆菌(*Limosilactobacillus reuteri*) CCFM1190 和长双歧杆菌(*Bifidobacterium longum*) CCFM1029 能缓解 FA 症状，3 种肠道菌群均能提高小鼠肠道菌群多样性，其中 CCFM1029 能增加肠道中产 SCFA 细菌的丰度，同时 CCFM1189 和 CCFM1190 处理后小鼠粪便中吲哚丙烯酸水平提高，检测发现 CCFM1189 和 CCFM1190 能使 FA 小鼠空肠组织中 IL-4、IL-5 和 IL13 水平降低，CCFM1189 和 CCFM1029 能使 FA 小鼠空肠组织中 IL-17 水平降低，通过以上途径达到抑制 Th2 免疫反应的目的。本课题组 Zhou 等的研究也发现，致敏小鼠肠道毛螺菌科(*Lachnospiraceae*)和梭菌科(*Clostridiaceae*)菌群的丰度与 MLN 中 Th2 细胞及其相关细胞因子 IL-4 的水平显著负相关[27]。这些研究结果均提示，肠道菌群可通过影响机体 Th 水平及其相关细胞因子来缓解或抑制食物过敏的发生和发展。

1.1.3 调节性 T 细胞

Treg 有维持人体免疫系统稳定、抑制 FA 发生的作用。在肠固有层中，$CD103^+$DCs 能摄取食物抗原并将其运输至附近淋巴结，在 TGF-β、视黄酸等佐剂作用下促进 DCs 与 $CD4^+$初始 T 细胞结合并促进其向 Treg 转化，从而诱导免疫耐受[32]。Li 等[33]发现长双歧杆菌婴儿亚种(*Bifidobacterium longum* subsp. *infantis*)含有一个独特的甲基化 CpG 序列，能诱导产生 Treg。研究发现，拟杆菌属(*Bacteroides*)的部分菌种能使 ROR-γt^+ Treg 数量增加，激活 ROR-γt^+ Treg，并以髓样分化因子 88 (myeloid differentiation primary response 88, Myd88)依赖的方式诱导转录因子 ROR-γt 表达，避免肠道 Treg 向 Th2 方向倾斜，从而降低 FA 的反应强度[34]。Liu 等[35]发现乳双歧杆菌(*Bifidobacterium lactis*)干预能减轻 FA 儿童的症状，动物实验发现乳双歧杆菌处理显著提高了 Treg 细胞相关因子 FoxP3 和 TGF-β 的表达，降低了 Th17 细胞相关因子 IL-17A 和 IL-23 的表达，从而抑制 FA 的发生，这与本课题组 Zhou 等[27]研究发现致敏小鼠肠道毛螺菌科(*Lachnospiraceae*)和梭菌科(*Clostridiaceae*)水平与 $Foxp3^+$ Treg 细胞水平显著正相关的结果一致。Verma 等[36]发现两歧双歧杆菌(*Bifidobacterium bifidum*)细胞表面的 β-葡聚糖/半乳聚糖(cell surface β-glucan/galactan, CSGG)是诱导 Treg 的关键成分，因此，单独使用 CSGG 也能发挥诱导 Treg 的作用。除细菌表面成分能发挥作用外，Paparo 等[37]研究发现，肠道菌群代谢产物丁酸盐能引起小鼠 MLN 和脾脏中 IL-4、IL-5 和 IL-13 水平显著降低，IFN-γ 和 IL-10 水平显著升高，同时诱导脾脏、MLN 和结肠中 $CD4^+CD25^+FoxP3^+$ Treg 水平的显著增加，有效抑制了小鼠的 FA 反应，这说明肠道菌群代谢物 SCFA 也能在诱导 Treg 中发挥一定作用。

1.1.4 肥大细胞

肥大细胞在 IgE 介导的 FA 中发挥重要作用。致敏原被机体免疫系统捕获后，被 APC 呈

递给 T 细胞，诱导 Th2 细胞的分化，并分泌 IL-4 和 IL-5 等细胞因子，这些细胞因子进而促进 B 细胞活化并产生致敏原特异性 IgE，特异性 IgE 与肥大细胞表面的 IgE Fc 受体I (Fc receptor of IgE I, FcεRI)结合使机体处于致敏状态，机体再次摄入致敏原时，致敏原与肥大细胞表面 FcεRI 结合的特异性 IgE 结合并产生交联反应，导致肥大细胞脱颗粒，释放组胺、中性蛋白酶和肝素等物质，引起过敏反应[32]。

研究发现，一些肠道菌群能以诱导肥大细胞凋亡等方式减少肥大细胞的数量，或抑制肥大细胞的脱颗粒来减轻 FA 症状。Kim 等[38]研究发现，长双歧杆菌 (*Bifidobacterium longum*) KACC 91563 干预能减轻 FA 小鼠的过敏症状，其肠道内肥大细胞数量及其产生的肥大细胞蛋白酶 1 (mast cell protease 1, MCPT-1)水平均显著减少，这与 Zhou 等发现的小鼠肠道中 *Mollicutes*_RF39 菌群的作用相似[27]。针对长双歧杆菌 KACC 91563 的深入研究发现，其细胞外囊泡 (extracellular vesicles, EVs)中含有家族 5 细胞外溶质结合蛋白 (family 5 extracellular solute-binding protein, ESBP)，EVs 被肥大细胞吞噬后，其中的 ESBP 可作用于肥大细胞促进其凋亡[38]。An 等[39]研究了长双歧杆菌 (*Bifidobacterium longum*)与 IgE 抗体 IgE_{TRAP} 联合作用对 FA 小鼠的治疗效果，结果显示 IgE_{TRAP} 能通过与 IgE 结合来降低其促进肥大细胞活化的作用，长双歧杆菌能在此基础上进一步减少肥大细胞数量，从而缓解小鼠 FA 症状。Folkerts 等[40]研究发现，肠道菌群的代谢产物丙酸盐和丁酸盐能有效抑制 FA 中肥大细胞的活化，丁酸盐通过显著降低布鲁顿酪氨酸激酶(Bruton's tyrosine kinase, BTK)、脾酪氨酸激酶(spleen tyrosine kinase, SYK)和 T 细胞活化接头蛋白(linker for activation of T cells, LAT)启动子区域乙酰化水平，诱导 BTK、SYK 和 LAT 等 FcεRI介导的信号通路中的关键物质表达水平下调，从而以浓度依赖的方式抑制 FA 中肥大细胞脱颗粒。

此外，某些肠道菌群还可能通过肥大细胞表面表达的 Toll 样受体(Toll-like receptor, TLR)[41]发挥作用。Kasakura 等[42]研究发现假小链双歧杆菌 (*Bifidobacterium pseudocatenulatum*) JCM 7041 能通过 TLR2 中断 FcεRI介导的细胞内信号来抑制肥大细胞的活化，从而发挥抗过敏作用。Tian 等[28,43]发现动物双歧杆菌(*Bifidobacterium animalis*) KV9 和阴道乳杆菌 (*Lactobacillus vaginalis*) FN3 使 FA 小鼠脾脏中 TLR4、Myd88、TRAF6、IκB 和 NF-κB 等 TLR4 及下游信号基因表达显著升高，此外，KV9 还可通过调节干扰素调节因子(interferon regulatory factor, IRF)的表达，激活过敏小鼠模型中的 TLR4 信号通路，抑制肥大细胞的聚集和活化，以及组胺的释放，促进 Th1/Th2 向 Th1 型的转变，从而抑制 FA。

1.1.5 粒细胞

粒细胞(granulocyte)是血液中的重要白细胞，在 IgE 介导的 FA 中可由原发性介质触发，中性粒细胞和嗜酸性粒细胞的聚集是 Th2 型免疫反应发生的重要标志，粒细胞等白细胞在肠壁聚集会加重肠道屏障的白细胞浸润，破坏正常肠道结构。Miranda 等[44]研究发现，嗜黏蛋白阿克曼氏菌(*Akkermansia muciniphila*) BAA-835 处理后肠道近端嗜酸性粒细胞趋化蛋白 CCL11/Eotaxin-1 和中性粒细胞趋化蛋白 CXCL1/KC 水平显著降低，减少了 FA 发生部位对嗜酸性粒细胞和中性粒细胞的募集。Santos 等[45]使用长双歧杆菌长亚种 (*Bifidobacterium longum* subsp. *longum*) 5^{1A} 处理的 OVA 致敏的小鼠后发现，小鼠近端空肠组织中嗜酸性过氧化物酶

(eosinophilic peroxidase)、髓过氧化物酶(myeloperoxidase)、CCL11/Eotaxin-1 和 CXCL1/KC 水平均低于对照组，同样说明肠道菌群处理减少了嗜酸性粒细胞和中性粒细胞在肠道的聚集，有益于减轻 FA 反应。

1.2 肠道菌群通过增强肠道屏障功能抑制食物过敏

FA 患儿摄入含有致敏原的食物后，致敏原通过肠道上皮细胞进入人体内环境，继而引发一系列的过敏反应。有研究者观察到 OVA 诱导 FA 后，小鼠空肠组织结构明显损伤，出现肠绒毛缺失、炎症浸润、固有层松动等肠道症状[46]。在人群研究中也发现牛奶过敏(cow milk allergy, CMA)患儿 Ki-67 和增殖细胞核抗原(proliferating cell nuclear antigen, PCNA)表达明显降低，肠黏膜组织中 Claudin-1、Claudin-3 和 MUC2 表达降低，肠屏障完整性受到破坏[8]。Zhang 等[47]研究发现抗生素引发的小鼠肠道菌群丰度和多样性降低会进一步导致其 FA 加重，在小鼠肠道发生肠绒毛破裂，同时紧密连接蛋白减少。因此，FA 患者通常伴随肠道结构的损伤和肠道屏障功能的降低，肠道菌群可能通过影响肠道屏障功能调节 FA 的发生。

肠道菌群能通过增强肠上皮细胞之间的紧密连接防止致敏原进入内环境。Gao 等[46]研究发现 FA 小鼠空肠组织损伤的主要原因是构成上皮细胞间紧密连接蛋白闭锁小带蛋白 1 (zonula occludin-1, ZO-1)和 *occludin* 基因表达显著下调，而肠膜状明串珠菌(*Leuconostoc mesenteroides*) WHH1141 能使这 2 种紧密连接蛋白基因表达趋于正常，以此来维持肠道结构的稳定并保障肠道屏障功能，口服 WHH1141 一段时间后，FA 小鼠症状和血清 IgE 水平明显改善。Chen 等[48]的研究也显示相似的结果，口服副干酪乳杆菌(*Lactobacillus paracasei*) AH2 能显著抑制麸质诱导的小鼠 FA，显著降低 FA 小鼠血清 sIgA、sIgG2a、sIgE 和组胺水平，进一步研究发现，AH2 能上调肠上皮紧密连接蛋白 Claudin 和 ZO-1 的表达水平，从而加强肠上皮细胞间的连接，减少进入血液循环系统的致敏原，从而抑制 FA 的发生。Jiang 等[49]研究发现植物乳植杆菌(*Lactiplantibacillus plantarum*) HM-22 干预能增强小鼠结肠紧密连接蛋白 occludin 和 Claudin-1 的表达，从而维持小鼠肠道屏障功能，降低 α-乳清蛋白(α-lactalbumin, α-LA)过敏导致的肠道通透性的增强，缓解 α-LA 过敏小鼠的体重减轻和脾脏、肝脏指数的升高。

另外，肠道菌群还能通过促进细胞因子的分泌降低肠道通透性。Kemter 等[50]研究发现，梭菌纲(*Clostridia*)能在 FA 中发挥保护作用，梭菌纲细菌的鞭毛能被肠道 $CD11c^{+}$APC 识别，通过 DCs 的 TLR5 和 MyD88 信号通路作用于 $ROR\gamma t^{+}$ 细胞的 AhR 通路诱导其产生 IL-22，而 IL-22 能降低肠道的通透性；同时梭菌纲能在肠道内分泌吲哚，吲哚在增强肠道屏障的保护作用的同时，还能依赖 $ROR\gamma t^{+}$细胞的 AhR 信号通路促进 IL-22 的产生。

2 益生菌和益生元在防治儿童食物过敏中的应用

益生菌是指对宿主健康有益的活体微生物，大量关于肠道菌群和 FA 的动物实验研究已经证实，外源益生菌干预能改善 FA 症状。有临床研究发现妊娠晚期携带霍尔德曼菌属(*Holdemania*)的母亲与其后代较低的 FA 患病率

有强相关性[51]，Cheng 等[52]进行的动物实验发现，向怀孕的小鼠灌胃两歧双歧杆菌(*Bifidobacterium bifidum*) TMC3115 后，其后代的肠道菌群丰度与结构均与对照组存在显著差异，实验组小鼠 OVA 致敏后血清 OVA 特异性 IgG1 水平显著低于对照组，而 IgM 和 sIgA 水平显著高于对照组，Ki67、Muc2、ZO-1、Claudin-1、Claudin-2 和 occludin 等肠道屏障功能相关蛋白 mRNA 表达水平显著高于对照组，这说明母体肠道菌群可影响后代 FA 的发生，针对母体进行益生菌干预治疗可能对后代 FA 起到预防作用。

益生元是指宿主体内可被有益微生物分解利用的底物，能促进特定微生物的生长和繁殖[53]。研究发现，矢车菊素-3-O-葡萄糖苷(cyanidin-3-O-glucoside)灌胃 OVA 致敏的小鼠后，小鼠肠道菌群中乳杆菌属(*Lactobacillus*)和臭气杆菌属(*Odoribacter*)丰度明显增加，螺杆菌属(*Helicobacter*)和苏黎世杆菌属(*Turicibacter*)丰度明显减少，同时，小鼠 FA 症状得到有效缓解[54]。Selle 等[55]的研究结果显示，向母体小鼠补充低聚半乳糖/菊粉(galacto-oligosaccharide/inulin)益生元后，后代小鼠接触小麦致敏原产生的 sIgG2a、sIgA 等抗炎 Ig 水平显著高于对照组，FA 相关抗体 IgG1 水平较对照组显著降低，小鼠 FA 的症状也得到改善。这说明益生元能通过影响宿主肠道菌群的丰度和结构缓解 FA，针对母体的益生元治疗也可能对后代的 FA 起到预防或缓解作用。

随着肠道菌群在儿童 FA 中的作用相关研究的深入，将益生菌或益生元应用于儿童 FA 的预防和治疗或将成为可能。世界过敏组织(World Allergy Organization, WAO)联合麦克马斯特大学(McMaster University)于 2016 年发布了关于益生元在过敏性疾病预防和治疗中应用的指南[56]，建议在非纯母乳喂养婴儿中补充益生元，而在纯母乳喂养的婴儿中不使用益生元补充剂，同时指出现有的孕妇或哺乳期母亲补充益生元的研究结果较少，无法支持该指南给出关于孕期或哺乳期益生元补充的建议。欧洲变态反应与临床免疫学会(European Academy of Allergy and Clinical Immunology, EAACI)于 2020 年更新了一份预防婴幼儿 FA 的指南[57]，该指南回顾了应用益生元、益生菌和两者混合物干预婴幼儿 FA 的相关临床试验，指出相关临床试验作为证据的确定性很低，EAACI 无法通过对应用益生元和益生菌等预防婴幼儿 FA 给出明确的建议。Fox 等[58]对益生元和益生菌在 CMA 中的应用及其作用机制进行回顾研究后，认为益生元和益生菌在儿童 CMA 中的应用仍需进一步探索。表 1 总结了近年采用益生菌或益生元预防或辅助治疗儿童 FA 的临床研究，但其在儿童 FA 预防和辅助治疗中的临床效果仍未明确。

3 展望及总结

FA 在儿童中广泛存在，可能导致严重后果，已对全球儿童健康造成一定威胁。本课题组赵童等进行的一项人群调查[73]发现，成年鸡蛋过敏人群肠道菌群中 β 变形菌目(*Betaproteobacteriales*)、伯克霍尔德氏菌科(*Burkholderiaceae*)和真杆菌属(*Eubacterium*)等与健康人群相比显著富集。因此，肠道菌群在儿童和成人 FA 发展中均起到了重要作用，通过调整肠道菌群的方式尽早干预儿童 FA 可能长远地使儿童获益。随着对 FA 致病机理研究的越发深入，人们在益生菌或益生元辅助治疗或预防儿童 FA 的应用中也进行了一些尝试，但目前对儿童 FA 仍缺乏可被广泛使用的有效治疗方法。

✉ actamicro@im.ac.cn, ☎ 010-64807516

表 1　近年与益生菌或益生元预防或辅助治疗儿童食物过敏有关的临床研究

Table 1　Recent clinical research related to probiotics or prebiotics for the prevention or adjuvant treatment of food allergies in children

Study	Prebiotics/Probiotics	Intervention methods	Study objects	Intervention duration	Results
Yamamoto-Hanada et al. 2023[59]	*Lactiplantibacillus plantarum* YIT 0132 (LP0132)	Drink inactivated citrus juice fermented with LP0132	Children aged 1−18 with IgE-mediated CMA	24 weeks	(1) Symptoms: There was no significant difference in the threshold CM doses between the LP0132 and control groups (2) Humoral immunity: There was no significant difference between the LP0132 and control groups in the level of sIgE and sIgG4 at the beginning and end of the intervention; the level of sIgG4 after probiotic intervention in the LP0132 group was significantly decreased compared with that before the intervention (3) Cellular immunity: Compared with before intervention, the serum level of IL-4 and IL-5 in the LP0132 group decreased significantly; at the end of the intervention, serum IL-5 and IL-9 levels were significantly lower in the LP0132 group than in the control group (4) Gut microbiota: The alpha diversity of gut microbiota and the genus proportion of *Lachnospiraceae* increased significantly in the LP0132 group
Komulainen et al. 2023[60]	*Lacticaseibacillus rhamnosus* HN001 and *Bifidobacterium animalis* ssp. *lactis* 420	Take probiotic capsules	Pregnant women with prepregnancy BMI≥25 kg/m^2, gestational age<18 weeks, and absence of chronic diseases (allergic diseases allowed)	24 months	(1) Symptoms: No significant difference between the infants in the intervention and control groups were found regarding physician-diagnosed FA at the age of 12 or 24 months
Kubota et al. 2023[61]	1-kestose	Take 1-kestose orally	Children with CMA	Median: 82 (range: 66–87) days	(1) Symptoms: There was no significant change in eczema score and treatment; the index for the OFC was decreased without significance (2) Humoral immunity: There were no significant changes in total IgE, CM-sIgE and casei-sIgG4 (3) Gut microbiota: The proportion of *Faecalibacterium* spp. in fecal sample collected from the subjects significantly increased after intervention

(待续)

(续表 1)

Study	Prebiotics/Probiotics	Intervention methods	Study objects	Intervention duration	Results
Wilsey et al. 2023[62]	LGG	Formula	Infants≤6 months with suspected or diagnosed CMA	Mean: 1.1 months	Symptoms: Compared with before the intervention, there were significant improvements in gastrointestinal, skin, and other symptoms after the invention; the respiratory symptoms yielded a significant improvement in the chronic cough and nasal obstruction symptoms only
Strisciuglio et al. 2023[63]	*Bifidobacterium longum* BB536, *Bifidobacterium infantis* M-63 and *Bifidobacterium breve* M-16V	Formula with probiotic mixture	Infants 0.5−12 months of age with diagnosed IgE-mediated CMA	45 days	Cellular immunity: After intervention, there was a significant decrease of circulating naive T lymphocytes; among the $CD3^+$ cell subsets, both naive and activated $CD4^+$ cells significantly reduced after taking probiotics
Chatchatee et al. 2022[64]	Oligosaccharides (oligofructose, inulin); *Bifidobacterium breve* M-16V	Formula	Infants<13 months with IgE-mediated CMA	24 months	(1) Symptoms: At 6 and 12 months of interventions, clinical symptoms decreased in both of intervention and control groups, and there was no significant difference between two groups; after 12 and 24 months, CM tolerance was not different between two groups (2) Gut microbiota: In the intervention group, the mean percentages of bifidobacteria were significantly higher at 6 and 12 months compared to those in the control group
Cukrowska et al. 2021[65]	*Lactobacillus rhamnosus* ŁOCK 0900, *Lactobacillus rhamnosus* ŁOCK 0908 and *Lactobacillus casei* ŁOCK 0919	A mixture of three probiotic strains	Children<2 years old with AD and CMA	3 months	(1) Symptoms: The probiotic and placebo groups did not differ significantly in terms of symptoms changes after the three-month intervention and the nine-month follow-up, but the symptoms improvement of probiotic group was better after the three-month intervention (2) Humoral immunity: After the nine-month follow-up, both groups showed increased total IgE level, but the intergroup difference of total IgE and sIgE was not statistically significant
Kuitnuen et al. 2009[66] Peldan et al. 2020[67]	Pregnant mothers: LGG, *Bifidobacterium breve* Bb99 and *Propionibacterium freudenreichii* ssp. shermanii JS; infants: LGG, *Bifidobacterium breve* Bb99 and *Propionibacterium freudenreichii* ssp. shermanii JS; galacto-oligosaccharides	Pregnant mothers: capsules containing freeze-dried probiotics; infants: capsules containing freeze-dried probiotics and prebiotics syrup	Pregnant mothers carrying a fetus with a high-risk of allergy (at least one of the parents had physician-diagnosed allergic disease)	Pregnant mothers: from 36 weeks of gestation until delivery; infants: from birth to 6 months	(1) Symptoms: At age of 5, no significant difference of allergic and IgE-associated allergic disease were detectable; cesarean-delivered children supplemented with probiotics had significantly fewer IgE-associated allergic diseases, particularly eczema, and less IgE sensitization; in vaginally delivered children no significant differences appeared between treatment groups (2) Humoral immunity: No significant difference were found in the prevalence of IgE sensitization to egg and/or milk at 2, 5, or 13 years old in the two groups

(待续)

(续表 1)

Study	Prebiotics/Probiotics	Intervention methods	Study objects	Intervention duration	Results
Jing et al. 2020[68]	*Bifidobacterium bifidum* TMC3115	Saline solution containing probiotics	Infants with CMA	6 months	(1) Symptoms: The allergic symptom scores were significantly different between the two groups at the primary timepoint for gastrointestinal tract, respiratory tract, skin, and whole-body allergic reaction; the total effective rate significantly increased in the intervention group when compared with the control group (2) Humoral immunity: The serum level of IgE in the intervention group was significantly lower than that in the control group; the serum level of IgG2a in the intervention group was significantly higher than that in the control group (3) Cellular immunity: The serum levels of TNT-α, IL-1, and IL-6 in the intervention group were significantly lower than those in the control group, and the serum level of IL-10 in the intervention group was significantly higher than that in the control group (4) Gut microbiota: Abundance and uniformity of gut microbiota in the intervention group were significantly higher than those in the control group; compared with the control group, the genus proportion of *Lactobacillus*, *Alistipes* and *Barnesiella* are significantly increased, the genus proportion of *Anaerovibrio*, *Christensenellaceae*, *Oscillibacter*, *Bilophila*, *Dorea*, and *Roseburia* is significantly reduced; after intervention, the genus proportion of *Bifidobacterium* significantly increased in the intervention group
Basturk et al. 2020[69]	LGG	Drops containing probiotics	Infants aged 0−12 months with diagnosed CMA	4 weeks	Symptoms: In the probiotic group, bloody stool, diarrhea, restiveness and abdominal distention were significantly improved, mucousy stool and vomiting were improved; in the placebo group, abdominal pain was significantly improved, bloody stool and restiveness were improved; the recovery situation in the two groups had no significant difference

(待续)

✉ actamicro@im.ac.cn, ☎ 010-64807516

(续表 1)

Study	Prebiotics/Probiotics	Intervention methods	Study objects	Intervention duration	Results
Chen et al. 2020[70]	*Bifidobacterium*	*Bifidobacterium* triple viable preparation	Infants with diagnosed FA	3 months	(1) Symptoms: After 6 and 12 months of follow-up, there was no significant difference in the incidence of eczema, wheezing or persistent cough in the past half year, asthma and allergic rhinitis between the standard intervention group and the standard intervention plus probiotics group (2) Cellular immunity: Compared with non-standard or non-intervention group, the eosinophils percentages and the TGF-βl levels in peripheral blood in standard intervention group and standard intervention with probiotics addition group were significantly decreased
Nocerino et al. 2019[71]	LGG	Formula	Children aged 4−6 years with a previous positive clinical history of CMA	/	Symptoms: In children with CMA treated with LGG, the incidence of functional gastrointestinal disorders was significantly lower compared to other CMA children, and was similar to that in healthy children
Candy et al. 2018[72]	Chicory-derived neutral oligofructose and long-chain inulin; *Bifidobacterium breve* M-16 V	Formula	Infants aged<13 months and had a clinical history or strong suspicion of non-IgE-mediated CMA	8 weeks	(1) Symptoms: Clinical symptoms had no significant difference between two groups (2) Gut microbiota: The median percentage of *Bifidobacteria* was significantly higher in the test group than in the control group; the *Eubacterium rectale*/*Clostridium coccoides* in the test group was significantly lower than the control group

CMA: Cow milk allergy; FA: Food allergy; OFC: Oral food challenge; LGG: *Lactobacillus rhamnosus* GG; CM: Cow milk; AD: Atopic dermatitis. /: Not mentioned.

由于肠道微生物群落的复杂性，许多菌属在进入肠道环境后会改变整个肠道微生物群落的结构。Duan 等[74]研究发现口服植物乳植杆菌(*Lactiplantibacillus plantarum*) JC7 能改善 OVA 致敏小鼠的 FA 症状，改善盲肠菌群的丰富度、多样性和均匀性，提高盲肠段拟杆菌门(*Bacteroidetes*)的丰度，并降低厚壁菌门(*Firmicutes*)丰度；Sun 等[75]发现双歧杆菌属(*Bifidobacterium*)在 CTLA-4 阻断的病理状态小鼠肠道中定殖后会以 Treg 依赖的方式显著增加乳杆菌属(*Lactobacillus*)、小浴氏菌属(*Kosakonia*)和克洛诺斯杆菌属(*Cronobacter*)的丰度等。尽管已有不少相关研究，现阶段的肠道菌群与 FA 相关研究多集中在单个种属或菌种对 FA 的影响及其机制，目前尚缺乏多种菌群间相互作用对 FA 的影响及机制相关研究。

此外，益生菌在治疗儿童 FA 中的应用也需进一步探索。从近年来益生菌或益生元在临床研究中发挥的作用来看，其应用效果并不十分理想。许多动物实验结果表明，通过粪菌移植(fecal microbiota transplantation, FMT)在肠道内定殖益生菌能缓解动物的 FA 症状，但这在人群临床试验中尚未得到验证[76]，可能是由人类生活习惯和膳食模式的多样性和复杂性导致的。除益生菌和益生元外，人们还研究了后生元(对宿主健康有益的无生命微生物和/或其成分[53])在治疗 FA 中的应用。研究表明，经高温杀灭的嗜黏蛋白阿克曼氏菌(*Akkermansia muciniphila*) BAA-835 与其活菌在缓解 OVA 致敏的小鼠过敏症状方面能起到相似作用，二者均能降低 FA 小鼠抗 OVA sIgE 水平并减少嗜酸性粒细胞聚集[40]。然而，也有研究结果显示，10^4 菌落形成单位(colony forming unit, CFU)剂量的活体长双歧杆菌长亚种(*Bifidobacterium longum* subsp. *longum*) 5^{1A} ($BL5^{1A}$)能显著降低 OVA 致敏小鼠肠道通透性，10^6 CFU 剂量活体 $BL5^{1A}$ 能在此基础上显著降低其肠道 sIgA 水平，10^8 CFU 剂量活体 $BL5^{1A}$ 在前两种作用基础上还能显著降低其血清 sIgE 水平，但使用 10^8 CFU 剂量的灭活 $BL5^{1A}$ 无法观察到任何对小鼠 OVA 过敏的缓解作用[45]，因此，后生元在 FA 缓解或治疗中的作用还存在争议。

综上所述，目前对于肠道菌群在婴幼儿及儿童 FA 中作用的研究及通过益生菌干预治疗或缓解儿童 FA 相关临床应用的研究都还处于探索阶段，而且多数研究在实验动物中进行，这些研究结果是否适用于人体还有待验证。因此，我们还需要更多深入研究来了解肠道菌群在儿童 FA 中充当的角色，来加速其临床应用及 FA 治疗相关策略和方法的开发，以助力人类攻克儿童 FA。

参考文献

[1] 周薇, 赵京, 车会莲, 洪建国, 洪莉, 李宏, 李在玲, 孟娟, 沙莉, 邵洁, 申昆玲, 王良录, 向莉, 邢嬛, 边赛男, 姜楠楠, 景红, 刘玲, 周鹏翔, 朱巍巍. 中国儿童食物过敏循证指南[J]. 中华实用儿科临床杂志, 2022, 37(8): 572-583.
ZHOU W, ZHAO J, CHE HL, HONG JG, HONG L, LI H, LI ZL, MENG J, SHA L, SHAO J, SHEN KL, WANG LL, XIANG L, XING H, BIAN SN, JIANG NN, JING H, LIU L, ZHOU PX, ZHU WW. Evidence-based guidelines for food allergy of children in China[J]. Chinese Journal of Applied Clinical Pediatrics, 2022, 37(8): 572-583 (in Chinese).

[2] CHAFEN JJ, NEWBERRY SJ, RIEDL MA, BRAVATA DM, MAGLIONE M, SUTTORP MJ, SUNDARAM V, PAIGE NM, TOWFIGH A, HULLEY BJ, SHEKELLE PG. Diagnosing and managing common food allergies: a systematic review[J]. JAMA, 2010, 303(18): 1848-1856.

[3] SHA L, SHAO MJ, LIU CH, WU YN, CHEN YZ. A cross-sectional study of the prevalence of food allergies among children younger than ages 14 years in a Beijing urban region[J]. Allergy and Asthma Proceedings, 2019, 40(1): e1-e7.

[4] ZABLOTSKY B, BLACK LI, AKINBAMI LJ. Diagnosed allergic conditions in children aged 0−17 years: United States, 2021[J]. NCHS Data Brief, 2023(459): 1-8.

[5] de JONG NW, ELBERT NJ, MENSINK-BOUT SM, van der VALK JPM, PASMANS SGMA, JADDOE VWV, de JONGSTE JC, van WIJK RG, DUIJTS L. Parental and child factors associated with inhalant and food allergy in a population-based prospective cohort study: the generation R study[J]. European Journal of Pediatrics, 2019, 178(10): 1507-1517.

[6] FENG H, CHEN Y, CHEN HB, LIU CW, ZHOU W, WANG LL, WU YN. A methodology of epidemiologic study in the general population focusing on food allergy: China, 2020[J]. China CDC Weekly, 2022, 4(34): 749-755.

[7] LUO JZ, ZHANG QY, GU YJ, WANG JJ, LIU GR, HE T, CHE HL. Meta-analysis: prevalence of food allergy and food allergens: China, 2000−2021[J]. China CDC Weekly, 2022, 4(34): 766-770.

[8] YU ZD, YUE LL, YANG ZJ, WANG YS, WANG ZH, ZHOU F, LI C, LI LF, ZHANG WC, LI XQ. Impairment of intestinal barrier associated with the alternation of intestinal flora and its metabolites in cow's milk protein allergy[J]. Microbial Pathogenesis, 2023, 183: 106329.

[9] PRESCOTT SL, PAWANKAR R, ALLEN KJ, CAMPBELL DE, SINN JK, FIOCCHI A, EBISAWA M, SAMPSON HA, BEYER K, LEE BW. A global survey of changing patterns of food allergy burden in children[J]. The World Allergy Organization Journal, 2013, 6(1): 21.

[10] GUPTA RS, SPRINGSTON EE, WARRIER MR, SMITH B, KUMAR R, PONGRACIC J, HOLL JL. The prevalence, severity, and distribution of childhood food allergy in the United States[J]. Pediatrics, 2011, 128(1): e9-e17.

[11] TEDNER SG, ASARNOJ A, THULIN H, WESTMAN M, KONRADSEN JR, NILSSON C. Food allergy and hypersensitivity reactions in children and adults: a review[J]. Journal of Internal Medicine, 2022, 291(3): 283-302.

[12] STRACHAN DP. Hay fever, hygiene, and household size[J]. British Medical Journal, 1989, 299(6710): 1259-1260.

[13] 林新鎏, 郑振宇, 任霞, 杨朝崴, 苏钟, 李靖. 环境暴露在过敏性疾病中的重要作用[J]. 中华临床免疫和变态反应杂志, 2019, 13(4): 276-282.
LIN XL, ZHENG ZY, REN X, YANG ZW, SU Z, LI J. Role of environmental factors in pathogenesis of allergic diseases[J]. Chinese Journal of Allergy & Clinical Immunology, 2019, 13(4): 276-282 (in Chinese).

[14] MUELLER NT, DIFFERDING MK, SUN HP, WANG JC, LEVY S, DEOPUJARI V, APPEL LJ, BLASER MJ, KUNDU T, SHAH AA, DOMINGUEZ BELLO MG, HOURIGAN SK. Maternal bacterial engraftment in multiple body sites of cesarean section born neonates after vaginal seeding: a randomized controlled trial[J]. mBio, 2023, 14(3): e0049123.

[15] RACHID R, STEPHEN-VICTOR E, CHATILA TA. The microbial origins of food allergy[J]. The Journal of Allergy and Clinical Immunology, 2021, 147(3): 808-813.

[16] FAZLOLLAHI M, CHUN Y, GRISHIN A, WOOD RA, BURKS AW, DAWSON P, JONES SM, LEUNG DYM, SAMPSON HA, SICHERER SH, BUNYAVANICH S. Early-life gut microbiome and egg allergy[J]. Allergy, 2018, 73(7): 1515-1524.

[17] BUNYAVANICH S, SHEN N, GRISHIN A, WOOD R, BURKS W, DAWSON P, JONES SM, LEUNG DYM, SAMPSON H, SICHERER S, CLEMENTE JC. Early-life gut microbiome composition and milk allergy resolution[J]. The Journal of Allergy and Clinical Immunology, 2016, 138(4): 1122-1130.

[18] CHUN Y, GRISHIN A, ROSE R, ZHAO W, ARDITI Z, ZHANG LD, WOOD RA, BURKS AW, JONES SM, LEUNG DYM, JONES DR, SAMPSON HA, SICHERER SH, BUNYAVANICH S. Longitudinal dynamics of the gut microbiome and metabolome in peanut allergy development[J]. The Journal of Allergy and Clinical Immunology, 2023, 152(6): 1569-1580.

[19] BAO RY, HESSER LA, HE ZY, ZHOU XY, NADEAU KC, NAGLER CR. Fecal microbiome and metabolome differ in healthy and food-allergic twins[J]. The Journal of Clinical Investigation, 2021, 131(2): e141935.

[20] 李心悦, 王硕, 张华, 李在玲. 牛奶蛋白过敏婴儿肠道菌群动态变化特点[J]. 临床儿科杂志, 2022, 40(11): 831-838.
LI XY, WANG S, ZHANG H, LI ZL. Characteristics of dynamic changes in the gut microbiome of infants with cow's milk protein allergy[J]. Journal of Clinical Pediatrics, 2022, 40(11): 831-838 (in Chinese).

[21] ZHANG LD, CHUN Y, HO HE, ARDITI Z, LO T, SAJJA S, ROSE R, JONES D, WANG JL, SICHERER S, BUNYAVANICH S. Multiscale study of the oral and gut environments in children with high- and low-threshold peanut allergy[J]. The Journal of Allergy and Clinical Immunology, 2022, 150(3): 714-720.e2.

[22] IWEALA OI, NAGLER CR. The microbiome and food allergy[J]. Annual Review of Immunology, 2019, 37: 377-403.

[23] KIM CH. Complex regulatory effects of gut microbial short-chain fatty acids on immune tolerance and autoimmunity[J]. Cellular & Molecular Immunology, 2023, 20: 341-350.

[24] LOUIS P, FLINT HJ. Formation of propionate and butyrate by the human colonic microbiota[J]. Environmental microbiology, 2017, 19(1): 29-41.

[25] TAN JK, MACIA L, MACKAY CR. Dietary fiber and SCFAs in the regulation of mucosal immunity[J]. The Journal of Allergy and Clinical Immunology, 2023, 151(2): 361-370.

[26] SMIT JJ, BOL-SCHOENMAKERS M, HASSING I, FIECHTER D, BOON L, BLEUMINK R, PIETERS RHH. The role of intestinal dendritic cells subsets in the establishment of food allergy[J]. Clinical and Experimental Allergy: Journal of the British Society for Allergy and Clinical Immunology, 2011, 41(6): 890-898.

[27] ZHOU C, CHEN LL, LU RQ, MA WW, XIAO R. Alteration of intestinal microbiota composition in oral sensitized C3H/HeJ mice is associated with changes in dendritic cells and T cells in mesenteric lymph nodes[J]. Frontiers in Immunology, 2021, 12: 631494.

[28] TIAN XY, FAN RB, HE H, CUI QY, LIANG X, LIU QQ, LIU TJ, LIN K, ZHANG Z, YI HX, GONG PM, ZHANG LW. *Bifidobacterium animalis* KV9 and *Lactobacillus vaginalis* FN3 alleviated β-lactoglobulin-induced allergy by modulating dendritic cells in mice[J]. Frontiers in Immunology, 2022, 13: 992605.

[29] FU LL, XIE MH, WANG C, QIAN Y, HUANG JJ, SUN ZH, ZHANG HP, WANG YB. *Lactobacillus casei* Zhang alleviates shrimp tropomyosin-induced food allergy by switching antibody isotypes through the NF-κB-dependent immune tolerance[J]. Molecular Nutrition & Food Research, 2020, 64(10): e1900496.

[30] CHEN XX, ZHAO XL, HU YZ, ZHANG BW, ZHANG Y, WANG S. *Lactobacillus rhamnosus* GG alleviates β-conglycinin-induced allergy by regulating the T cell receptor signaling pathway[J]. Food & Function, 2020, 11(12): 10554-10567.

[31] LU WW, QIAN L, FANG ZF, WANG HC, ZHU JL, LEE YK, ZHAO JX, ZHANG H, CHEN W. Probiotic strains alleviated OVA-induced food allergy in mice by regulating the gut microbiota and improving the level of indoleacrylic acid in fecal samples[J]. Food & Function, 2022, 13(6): 3704-3719.

[32] PALOMARES O. The role of regulatory T cells in IgE-mediated food allergy[J]. Journal of Investigational Allergology & Clinical Immunology, 2013, 23(6): 371-382.

[33] LI DM, CHENG J, ZHU ZA, CATALFAMO M, GOERLITZ D, LAWLESS OJ, TALLON L, SADZEWICZ L, CALDERONE R, BELLANTI JA. Treg-inducing capacity of genomic DNA of *Bifidobacterium longum* subsp. *infantis*[J]. Allergy and Asthma Proceedings, 2020, 41(5): 372-385.

[34] ABDEL-GADIR A, STEPHEN-VICTOR E, GERBER GK, NOVAL RIVAS M, WANG S, HARB H, WANG L, LI N, CRESTANI E, SPIELMAN S, SECOR W, BIEHL H, DiBENEDETTO N, DONG XX, UMETSU DT, BRY L, RACHID R, CHATILA TA. Microbiota therapy acts *via* a regulatory T cell MyD88/RORγt pathway to suppress food allergy[J]. Nature Medicine, 2019, 25: 1164-1174.

[35] LIU QB, JING W, WANG W. *Bifidobacterium lactis* ameliorates the risk of food allergy in Chinese children by affecting relative percentage of Treg and Th17 cells[J]. The Canadian Journal of Infectious Diseases & Medical Microbiology, 2018, 2018: 4561038.

[36] VERMA R, LEE C, JEUN EJ, YI J, KIM KS, GHOSH A, BYUN S, LEE CG, KANG HJ, KIM GC, JUN CD, JAN G, SUH CH, JUNG JY, SPRENT J, RUDRA D, de CASTRO C, MOLINARO A, SURH CD, IM SH. Cell surface polysaccharides of *Bifidobacterium bifidum* induce the generation of Foxp3^{+} regulatory T cells[J]. Science Immunology, 2018, 3(28): eaat6975.

[37] PAPARO L, NOCERINO R, CIAGLIA E, di SCALA C, de CARO C, RUSSO R, TRINCHESE G, AITORO R, AMOROSO A, BRUNO C, di COSTANZO M, PASSARIELLO A, MESSINA F, AGANGI A, NAPOLITANO M, VOTO L, GATTA G D, PISAPIA L, MONTELLA F, MOLLICA M P, et al. Butyrate as a bioactive human milk protective component against food allergy[J]. Allergy, 2021, 76(5): 1398-1415.

[38] KIM JH, JEUN EJ, HONG CP, KIM SH, JANG MS, LEE EJ, MOON SJ, YUN CH, IM SH, JEONG SG,

PARK BY, KIM KT, SEOH JY, KIM YK, OH SJ, HAM JS, YANG BG, JANG MH. Extracellular vesicle-derived protein from *Bifidobacterium longum* alleviates food allergy through mast cell suppression[J]. The Journal of Allergy and Clinical Immunology, 2016, 137(2): 507-516.e8.

[39] AN SB, YANG BG, JANG G, KIM DY, KIM J, OH SM, OH N, LEE S, MOON JY, KIM JA, KIM JH, SONG YJ, HYUN HW, KIM J, LEE K, LEE D, KWAK MJ, KIM BK, PARK YK, HONG CP, et al. Combined IgE neutralization and *Bifidobacterium longum* supplementation reduces the allergic response in models of food allergy[J]. Nature Communications, 2022, 13: 5669.

[40] FOLKERTS J, REDEGELD F, FOLKERTS G, BLOKHUIS B, van den BERG M, de BRUIJN M, van IJCKEN W, JUNT T, TAM SY, GALLI SJ, HENDRIKS RW, STADHOUDERS R, MAURER M. Butyrate inhibits human mast cell activation *via* epigenetic regulation of FcεRI-mediated signaling[J]. Allergy, 2020, 75(8): 1966-1978.

[41] AYALA-CUELLAR AP, CHO J, CHOI KC. Toll-like receptors: a pathway alluding to cancer control[J]. Journal of Cellular Physiology, 2019, 234(12): 21707-21715.

[42] KASAKURA K, TAKAHASHI K, AIZAWA T, HOSONO A, KAMINOGAWA S. A TLR2 ligand suppresses allergic inflammatory reactions by acting directly on mast cells[J]. International Archives of Allergy and Immunology, 2009, 150(4): 359-369.

[43] TIAN XY, LIANG X, HE H, CUI QY, LIU QQ, FAN RB, LIU TJ, YI HX, GONG PM, WANG QZ, ZHANG LW. Probiotics alleviate food protein allergy in mice by activating TLR4 signaling pathway[J]. Molecular Nutrition & Food Research, 2023, 67(12): e2200579.

[44] MIRANDA VC, SOUZA RO, QUINTANILHA MF, GALLOTTI B, ASSIS HC, FARIA AMC, NICOLI JR, CARA DC, MARTINS FS. A next-generation bacteria (*Akkermansia muciniphila* BAA-835) presents probiotic potential against ovalbumin-induced food allergy in mice[J]. Probiotics and Antimicrobial Proteins, 2024, 16(3): 737-751.

[45] SANTOS SS, MIRANDA VC, TRINDADE LM, CARDOSO VN, REIS DC, CASSALI GD, NICOLI JR, CARA DC, MARTINS FS. *Bifidobacterium longum* subsp. *longum* 5^{1A} attenuates signs of inflammation in a murine model of food allergy[J]. Probiotics and Antimicrobial Proteins, 2023, 15(1): 63-73.

[46] GAO K, CHEN L, CHEN CL, CHEN ZG, ZHANG QW, FAN QL, LI YJ, CHEN S. *Leuconostoc mesenteroides* WHH1141 ameliorates ovalbumin-induced food allergy in mice[J]. Journal of Food Science, 2023, 88(10): 4289-4304.

[47] ZHANG QY, CHENG L, WANG JJ, HAO MZ, CHE HL. Antibiotic-induced gut microbiota dysbiosis damages the intestinal barrier, increasing food allergy in adult mice[J]. Nutrients, 2021, 13(10): 3315.

[48] CHEN C, LIU CL, MU KY, XUE WT. *Lactobacillus paracasei* AH2 isolated from Chinese sourdough alleviated gluten-induced food allergy through modulating gut microbiota and promoting short-chain fatty acid accumulation in a BALB/c mouse model[J]. Journal of the Science of Food and Agriculture, 2024, 104(2): 664-674.

[49] JIANG SJ, HOU YQ, MENG LY, PU XL, ZHU XM, TUO YF, QIAN F, MU GQ. Effect of *Lactiplantibacillus plantarum* HM-22 on immunoregulation and intestinal microbiota in α-lactalbumin-induced allergic mice[J]. Food & Function, 2021, 12(19): 8887-8898.

[50] KEMTER AM, PATRY RT, ARNOLD J, HESSER LA, CAMPBELL E, IONESCU E, MIMEE M, WANG S, NAGLER CR. Commensal bacteria signal through TLR5 and AhR to improve barrier integrity and prevent allergic responses to food[J]. Cell Reports, 2023, 42(10): 113153.

[51] WANG S, ZHANG R, LI XY, GAO YJ, DAI NN, WEI Y, LIU LY, XING Y, LI ZL. Relationship between maternal-infant gut microbiota and infant food allergy[J]. Frontiers in Microbiology, 2022, 13: 933152.

[52] CHENG RY, ZHANG YJ, YANG Y, REN L, LI JX, WANG YM, SHEN X, HE F. Maternal gestational *Bifidobacterium bifidum* TMC3115 treatment shapes construction of offspring gut microbiota and development of immune system and induces immune tolerance to food allergen[J]. Frontiers in Cellular and Infection Microbiology, 2022, 12: 1045109.

[53] 黄福青, 云芳菲, 滕坤玲, 王天威, 钟瑾. 益生菌、益生元和后生元对食物过敏的影响和作用机制[J]. 微生物学报, 2022, 62(3): 848-857.
HUANG FQ, YUN FF, TENG KL, WANG TW, ZHONG J. The effects and functioning mechanisms of probiotics, prebiotics and postbiotics on food allergy[J]. Acta Microbiologica Sinica, 2022, 62(3): 848-857 (in Chinese).

[54] LI J, ZOU C, LIU YX. Amelioration of ovalbumin-induced food allergy in mice by targeted rectal and colonic delivery of cyanidin-3-O-glucoside[J]. Foods, 2022, 11(11): 1542.

[55] SELLE A, BROSSEAU C, DIJK W, DUVAL A, BOUCHAUD G, ROUSSEAUX A, BRUNEAU A, CHERBUY C, MARIADASSOU M, CARIOU V, BARBAROT S, BODINIER M. Prebiotic supplementation during gestation induces a tolerogenic environment and a protective microbiota in offspring mitigating food allergy[J]. Frontiers in Immunology, 2022, 12: 745535.

[56] FIOCCHI A, PAWANKAR R, CUELLO-GARCIA C, AHN K, AL-HAMMADI S, AGARWAL A, BEYER K, BURKS W, CANONICA GW, EBISAWA M, GANDHI S, KAMENWA R, LEE BW, LI HQ, PRESCOTT S, RIVA JJ, ROSENWASSER L, SAMPSON H, SPIGLER M, TERRACCIANO L, et al. World allergy organization-McMaster university guidelines for allergic disease prevention (GLAD-P): probiotics[J]. World Allergy Organization Journal, 2015, 8(1): 1-13.

[57] HALKEN S, MURARO A, de SILVA D, KHALEVA E, ANGIER E, ARASI S, ARSHAD H, BAHNSON HT, BEYER K, BOYLE R, du TOIT G, EBISAWA M, EIGENMANN P, GRIMSHAW K, HOEST A, JONES C, LACK G, NADEAU K, O'MAHONY L, SZAJEWSKA H, et al. EAACI guideline: preventing the development of food allergy in infants and young children (2020 update)[J]. Pediatric Allergy and Immunology: Official Publication of the European Society of Pediatric Allergy and Immunology, 2021, 32(5): 843-858.

[58] FOX A, BIRD JA, FIOCCHI A, KNOL J, MEYER R, SALMINEN S, GONG ST, SZAJEWSKA H, PAPADOPOULOS N. The potential for pre-, pro- and synbiotics in the management of infants at risk of cow's milk allergy or with cow's milk allergy: an exploration of the rationale, available evidence and remaining questions[J]. The World Allergy Organization Journal, 2019, 12(5): 100034.

[59] YAMAMOTO-HANADA K, SATO M, TOYOKUNI K, IRAHARA M, HIRAIDE-KOTAKI E, HARIMA-MIZUSAWA N, MORITA H, MATSUMOTO K, OHYA Y. Combination of heat-killed *Lactiplantibacillus plantarum* YIT 0132 (LP0132) and oral immunotherapy in cow's milk allergy: a randomised controlled trial[J]. Beneficial Microbes, 2023, 14(1): 17-29.

[60] KOMULAINEN M, SAROS L, VAHLBERG T, NERMES M, JARTTI T, LAITINEN K. Maternal fish oil and/or probiotics intervention: allergic diseases in children up to two years old[J]. Pediatric Allergy and Immunology: Official Publication of the European Society of Pediatric Allergy and Immunology, 2023, 34(8): e14004.

[61] KUBOTA S, SUGIURA S, TAKAHASHI M, KADOTA Y, TAKASATO Y, MATSUI T, KITAMURA K, TOCHIO T, ITO K. Kestose increases the relative abundance of *Faecalibacterium* spp. and nominally increases cow milk tolerant dose in children with cow's milk allergy-preliminary results[J]. Polish Journal of Microbiology, 2023, 72(3): 299-306.

[62] WILSEY MJ, FLORIO J, BEACKER J, LAMOS L, BARAN JV, OLIVEROS L, SRIAROON P, BROWN JM, VANDERHOOF JA. Extensively hydrolyzed formula improves allergic symptoms in the short term in infants with suspected cow's milk protein allergy[J]. Nutrients, 2023, 15(7): 1677.

[63] STRISCIUGLIO C, VITALE A, PERNA F, GARZIANO F, DOLCE P, VITALE S, MICILLO T, OGLIO F, del GIUDICE MM, MATARESE G, GIANFRANI C. *Bifidobacteria* modulate immune response in pediatric patients with cow's milk protein allergy[J]. Pediatric Research, 2023, 94: 1111-1118.

[64] CHATCHATEE P, NOWAK-WEGRZYN A, LANGE L, BENJAPONPITAK S, CHONG KW, SANGSUPAWANICH P, van AMPTING MTJ, OUDE NIJHUIS MM, HARTHOORN LF, LANGFORD JE, KNOL J, KNIPPING K, GARSSEN J, TRENDELENBURG V, PESEK R, DAVIS CM, MURARO A, ERLEWYN-LAJEUNESSE M, FOX AT, MICHAELIS LJ, et al. Tolerance development in cow's milk-allergic infants receiving amino acid-based formula: a randomized controlled trial[J]. The Journal of Allergy and Clinical Immunology, 2022, 149(2): 650-658.e5.

[65] CUKROWSKA B, CEREGRA A, MACIORKOWSKA E, SUROWSKA B, ZEGADŁO-MYLIK MA, KONOPKA E, TROJANOWSKA I, ZAKRZEWSKA M, BIERŁA JB, ZAKRZEWSKI M, KANAREK E, MOTYL I. The effectiveness of probiotic *Lactobacillus rhamnosus* and *Lactobacillus casei* strains in children with atopic dermatitis and cow's milk protein allergy: a multicenter, randomized, double blind, placebo controlled study[J]. Nutrients, 2021, 13(4): 1169.

[66] KUITUNEN M, KUKKONEN K, JUNTUNEN-BACKMAN K, KORPELA R, POUSSA T, TUURE T, HAAHTELA T, SAVILAHTI E. Probiotics prevent IgE-associated allergy until age 5 years in cesarean-delivered children but not in the total cohort[J]. The Journal of Allergy and Clinical Immunology, 2009, 123(2): 335-341.

[67] PELDAN PS, KUKKONEN AK, SAVILAHTI E, KUITUNEN M. Perinatal probiotic mixture and development of allergic sensitization up to 13 years of age[J]. International Archives of Allergy and Immunology, 2020, 181(4): 270-277.

[68] JING W, LIU QB, WANG W. *Bifidobacterium bifidum* TMC3115 ameliorates milk protein allergy in by affecting gut microbiota: a randomized double-blind control trial[J]. Journal of Food Biochemistry, 2020, 44(11): e13489.

[69] BASTURK A, ISIK İ, ATALAY A, YıLMAZ A. Investigation of the efficacy of *Lactobacillus rhamnosus* GG in infants with cow's milk protein allergy: a randomised double-blind placebo-controlled trial[J]. Probiotics and Antimicrobial Proteins, 2020, 12(1): 138-143.

[70] 陈昂, 王桂兰, 刘翔腾, 张泉山. 早期干预对食物过敏婴儿其他过敏性疾病发生的预防作用[J]. 吉林大学学报(医学版), 2020, 46(4): 851-857.
CHEN A, WANG GL, LIU XT, ZHANG QS. Preventive effect of early intervention on occurrence of other allergic diseases in infants with food allergy[J]. Journal of Jilin University (Medicine Edition), 2020, 46(4): 851-857 (in Chinese).

[71] NOCERINO R, di COSTANZO M, BEDOGNI G, COSENZA L, MADDALENA Y, di SCALA C, DELLA GATTA G, CARUCCI L, VOTO L, COPPOLA S, IANNICELLI AM, BERNI CANANI R. Dietary treatment with extensively hydrolyzed casein formula containing the probiotic *Lactobacillus rhamnosus* GG prevents the occurrence of functional gastrointestinal disorders in children with cow's milk allergy[J]. The Journal of Pediatrics, 2019, 213: 137-142.e2.

[72] CANDY DCA, van AMPTING MTJ, OUDE NIJHUIS MM, WOPEREIS H, BUTT AM, PERONI DG, VANDENPLAS Y, FOX AT, SHAH N, WEST CE, GARSSEN J, HARTHOORN LF, KNOL J, MICHAELIS LJ. A synbiotic-containing amino-acid-based formula improves gut microbiota in non-IgE-mediated allergic infants[J]. Pediatric Research, 2018, 83(3): 677-686.

[73] 赵童, 杨善平, 陈玲玲, 赵莲英, 刘冬青, 麻微微, 周催. 鸡蛋过敏人群肠道菌群特征及其与血清细胞因子的相关性[J/OL]. 食品科学, 2024[2024-03-18]. http://kns.cnki.net/kcms/detail/11.2206.TS.20240308.1433.054.html.
ZHAO T, YANG SP, CHEN LL, ZHAO LY, LIU DQ, MA WW, ZHOU C. Characterization of intestinal flora and its correlation with serum cytokines in egg-allergic population[J/OL]. Food Science, 2024[2024-03-18]. http://kns.cnki.net/kcms/detail/11.2206.TS.20240308.1433.054.html (in Chinese).

[74] DUAN CC, MA L, YU J, SUN YX, LIU LF, MA FM, LI XL, LI D. Oral administration of *Lactobacillus plantarum* JC7 alleviates OVA-induced murine food allergy through immunoregulation and restoring disordered intestinal microbiota[J]. European Journal of Nutrition, 2023, 62(2): 685-698.

[75] SUN S, LUO LJ, LIANG WH, YIN Q, GUO J, RUSH AM, LV ZB, LIANG QM, FISCHBACH MA, SONNENBURG JL, DODD D, DAVIS MM, WANG F. *Bifidobacterium* alters the gut microbiota and modulates the functional metabolism of T regulatory cells in the context of immune checkpoint blockade[J]. Proceedings of the National Academy of Sciences of the United States of America, 2020, 117(44): 27509-27515.

[76] POTO R, FUSCO W, RINNINELLA E, CINTONI M, KAITSAS F, RAOUL P, CARUSO C, MELE M C, VARRICCHI G, GASBARRINI A, CAMMAROTA G, IANIRO G. The Role of Gut Microbiota and Leaky Gut in the Pathogenesis of Food Allergy[J]. Nutrients, 2023, 16(1).