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生命早期微生物群的发育与人类的健康和疾病

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摘要

人类微生物群在生命早期的定植对健康具有长期的影响。最初肠道微生物群的状态决定了人类从婴儿期到成年期的生长发育，因此是人类长期发育的一个关键窗口期。本文旨在总结生命早期共生肠道微生物群的最新发现及其在代谢、过敏和自身免疫疾病相关的疾病（包括肥胖症、糖尿病、过敏性疾病、自闭症、炎症性肠病和发育迟缓）中的重要作用。本文讨论了肠道微生物群发育过程和塑造肠道微生物群的各种因素，以及肠道微生物群在生命早期建立过程中与宿主生理系统之间的串扰（尤其是肠道免疫发育和稳态，以及神经发育过程中的中枢神经系统），以破译与生命早期肠道微生物组相关的疾病机制。此外，还考察了以微生物群为靶向的治疗方法，并显示出这些方法对于上述疾病具有一定的治疗潜力。肠道微生物组正确的成熟过程取决于遗传、营养和环境因素，必须详细检查，以监测健康的肠道微生物组发育，并通过新型益生菌或粪便微生物群移植等方法进行干预，尽可能以此纠正错误的发育过程。

1. 引言

近几十年来，儿童健康保健中忧虑问题的流行和发病率持续增加，包括与代谢、过敏性疾病和自身免疫疾病相关的疾病[1–5]。然而，对这些疾病仍然缺乏有效的治疗手段。同时，抗生素等现代医学技术是一把“双刃剑”，对提高儿童疾病的存活率和降低发病率有很大的帮助，但会破坏儿童肠道内正常的微生物生态。儿科疾病的发生是多因素的，包括遗传[6–7]、感染[8–10]和免疫[11–14]。随着研究的进展，越来越多的证据表明生命早期的肠道微生物群是导致这些疾病的危险因素之一，这些疾病取决于遗传、营养和其他环境因素[15–17]。

人们普遍认为，人类微生物群在健康和疾病中起着重要作用[18]。现代生活方式，如母亲的饮食、出生时的胎龄、分娩方式、喂养方式和抗生素暴露都会干扰人类早期肠道微生物群的正常定植和成熟[19–20]。值得注意的是，微生物群的微生物干预包括益生菌和益生元的使用，已被证明是一种可以优化婴儿和儿童微生物群的潜在有效管理工具[21–24]。尽管益生菌在婴儿和儿童中的安全性需要进一步阐明[25–26]，但生命早期微生物群在人类生长发

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育中的角色正成为一个热门话题[27]，而其作用仍不明确。

人类早期微生物群是干预建立健康微生物群的关键“窗口”期，这是由于婴儿的肠道微生物群变化迅速，并在生命的前三年内达到相对稳定的状态[28–29]。胃肠道（GI）包含人体中最大和最多样化的细菌群落（通常是10^{11}~10^{12}个微生物·mL^{-1}）[29]。胃肠道可以促进生理发育的成熟（如维生素K的合成），并在人的一生中发挥免疫和病原体抗性的作用[17]。微生物失调已被证明会导致代谢异常和免疫紊乱，尤其在婴幼儿中。微生物失调会导致代谢、过敏和自身免疫失调相关疾病，如肥胖症[30]、1型糖尿病（T1D）[31]、过敏性疾病[32]、自闭症[33]、炎症性肠病（IBD）[34]和发育迟缓[19]。

除了生理功能外，在神经发育过程中，微生物群还参与儿童免疫系统和中枢神经系统（CNS）的健康发育，也引起了学术界的关注。首先，肠道中数量最多、种类最多的免疫细胞与数万亿微生物相遇[35]，这对宿主免疫稳态至关重要。肠道包含多个免疫细胞亚群，宿主的先天免疫在肠道中得到很好的协调。其次，肠道微生物群通过微生物群-肠-脑轴，对儿童中枢神经系统的贡献非常重要[36]。

研究表明，婴儿期的神经发育易受内部和外部微生物因素的影响[37–39]。例如，暴露于病原体（如空肠弯曲杆菌或埃希氏杆菌属）会导致幼鼠出现异常行为，包括焦虑样行为和记忆障碍[37–38]。此外，微生物代谢产物，即短链脂肪酸（SCFA）可以促进小胶质细胞的成熟，并帮助其维持正常功能[40]。此外，营养成分、益生菌、益生元低聚糖和某些氨基酸通过调节炎症和感染，对大脑的白质损伤具有神经保护作用（可能在早产后发生）[41]。

2. 从婴儿期到儿童期的肠道菌群特征

正常的肠道微生物群在人类健康中起着重要作用，包括营养获取、免疫调节、神经发育和行为[18,27,42]。婴儿期和儿童期是肠道菌群形成和成熟的最重要时期[43]。婴儿和儿童的主要微生物群在出生后的前三年迅速变化。例如，微生物群在出生后立即定植于婴儿的肠道，并且肠道微生物群的轨迹在所有婴儿中显示出多种相似性[43–45]。婴儿的肠道菌群会在1岁时达到成人样组成，婴儿可能需要2.5~3年的时间才能建立稳定的成人样肠道菌群[28,46]。在儿童体内建立稳定的微生物群之前，有三个不同的阶段：发育阶段（3~14个月）、过渡阶段（15~30个月）和稳定阶段（≥31个月）[47]。双歧杆菌是发育阶段的主要细菌[47–48]；Proteobacteria和Bacteroide在过渡阶段发生了显著变化[46–48]；Firmicutes在稳定阶段占主导地位[46–47,49]。此外，健康儿童富含双歧杆菌、粪杆菌和毛螺菌科，而成人则富含拟杆菌[27]。

从功能角度来看，非成人和成人之间在合成营养素、氨基酸降解、氧化磷酸化和黏膜炎症相关基因方面有很大不同[27]。儿童肠道微生物群更有可能支持与持续发育和抗炎特性相关的功能，包括维生素B12合成和叶酸代谢[48,50]。成人的肠道微生物群富含氧化磷酸化、脂多糖（LPS）生物合成、鞭毛组装和类固醇激素生物合成的基因[27,51–52]。成人微生物群的这些特征被怀疑是肥胖症和代谢紊乱发病率增加的原因[48,52]。

3. 从婴儿期到儿童期影响肠道菌群的因素

婴儿和儿童不同的微生物群定植模式影响他们后续一生中的免疫反应和潜在疾病发生率[53–55]。越来越多的证据表明，在儿童的发育阶段（2.5~3岁），某些因素可以影响肠道微生物群的结构和组成，包括母亲的产前状况、分娩方式、母乳喂养或奶瓶喂养、早期饮食和产后医疗干预措施[19,56]。

3.1. 分娩方式

分娩方式是生命早期建立健康微生物组的最重要决定因素。剖宫产分娩的新生儿首先被母亲的皮肤微生物群定植，这些新生儿各部位的微生物与其母亲的皮肤群落相似[57]。同样地，经阴道分娩的婴儿各部位的细菌群落都与母亲的阴道群落相似[57]。有趣的是，尽管剖腹产婴儿和阴道分娩婴儿在生命的前六个月表现出相似的微生物群成熟度，但与阴道分娩婴儿相比，剖腹产婴儿的微生物群成熟度在接下来的6个月中停滞不前[58]。在随后的一年中，剖腹产婴儿的微生物群多样性逐渐成熟，并与阴道分娩婴儿的微生物群相似[58]。然而，仍在不同分娩方式的婴儿的主要微生物群中观察到显著差异。例如，在出生后的前三个月，与阴道分娩的婴儿相比，剖腹产分娩的婴儿Actinobacteria和Bacteroidetes的水平较低，而Firmicute的水平较高，而阴道分娩的婴儿主要由*Bifidobacterium*、*Bacteroides*、*Clostridium*和*Lactobacillus*定植[55]。研究表明，与阴道分娩婴儿相比，剖腹产婴儿患T1D [59]、肥胖症[60]、哮喘[61]、乳糜泻[59]和儿童期死亡[61]的概率更高。因此，分娩方式会影响出生后婴儿第一年的肠道微生物群。

3.2. 喂养方式

喂养方式是生命早期肠道微生物组组成的另一个决定

性因素。众所周知，母乳喂养有利于婴儿肠道菌群的形成。母乳喂养可以直接为婴儿提供来自母亲的益生菌，同时通过给予婴儿人乳寡糖作为益生元，间接促进肠道中有益*Bifidobacterium*的生长[62–66]。母乳喂养婴儿的微生物组成与配方奶喂养婴儿的微生物组成不同[64,67]。在生命的前三个月，与母乳喂养的婴儿相比，配方奶喂养的婴儿的微生物群成熟度、系统发育多样性和细菌丰度的增长速度显著降低。在此期间，*Lactobacillus*、*Staphylococcus*、*Megasphaera*和Actinobacteria在母乳喂养的婴儿中含量更高，而Clostridiales和Proteobacteria在配方奶喂养的婴儿中含量更高[58]。研究发现，有益*Bifidobacterium*、*Lactobacillus*和*Clostridia*的丰度与母乳喂养呈正相关，与配方奶粉喂养呈负相关，母乳喂养婴儿的功能性Lachnospiraceae的丰度降低[68–69]。此外，大多数母乳喂养婴儿的肠道微生物组的合成蛋氨酸、支链氨基酸、半胱氨酸/丝氨酸、苏氨酸和精氨酸的能力增强[69]。研究表明，在引入固体食物之前，纯母乳喂养（EBF）婴儿的肠道微生物群相比非EBF婴儿的肠道微生物群有很大不同，其特点是*Bifidobacterium*丰度较高，而Bacteroidetes和Clostridiales丰度较低[70]。除了母乳喂养外，固体食物的摄入还导致微生物组成发生巨大变化，不仅表现在在向相对稳定的群落过渡方面，而且SCFA产量、维生素生物和碳水化合物合成都增加了[28]。有趣的是，辅食摄入的模式也会影响肠道微生物群。在细菌α-多样性和*Roseburia*丰度方面，12个月大的婴儿主导的固体食物摄入组（即婴儿主导的断奶改良方式，在6个月大时摄入固体食物，随后自主摄入家庭食物）比传统摄入方式组（即父母用勺子喂糊状食物）更低[71]。

3.3. 环境因素

环境因素，尤其是生命早期使用抗生素，会延迟肠道微生物群的成熟时间。例如，接触抗生素的儿童表现出比未接触抗生素的儿童更慢的肠道微生物群成熟；这在第6个月和第12个月之间最为明显，主要是由于缺乏Lachnospiraceae和Erysipelotrichaceae [58]。此外，用β-内酰胺或大环内酯进行早期脉冲抗生素治疗（PAT）可能会影响宿主肠道微生物群的代谢；这些影响包括减少糖酵解和糖异生途径并增加柠檬酸循环、核苷合成和氨基酸合成[72]。此外，在用低剂量青霉素处理小鼠的PAT中，*Lactobacillus*、*Candidatus Arthromitus*、*Allobaculum*的丰度降低，免疫相关基因表达发生改变，包括免疫细胞的分化、活化、黏附、募集和数量减少；这些影响会导致肥胖症并在其一生中继续影响宿主[73]。此外，早期抗生素暴露引起的改变使宿主易患疾病，如肥胖症[74–75]、T1D [76]和哮喘[77]。

4. 肠道菌群对肠道稳态和神经发育的影响

4.1. 微生物群及其代谢产物对肠道发育和稳态的作用机制

肠道微生物群是人类健康和福祉的关键因素。首先，肠道微生物群促进肠道成熟[78]。新生儿胃肠道的结构和功能尚不成熟[79]。肠道微生物群通过调节营养代谢、上皮屏障完整性和免疫力，在免疫系统的发展中发挥着至关重要的作用，尤其在肠道稳态维持中[79–81]。多种肠道细菌和肠道来源的代谢物参与维持肠道稳态，包括对外来病原体入侵的抵抗和抗炎维持稳态（图1）。在众多共生微生物群中，分段丝状细菌（SFB）是调节肠道稳态免疫反应特别重要的肠道微生物[82–83]。T细胞和B细胞是适应性免疫应答的主要细胞成分。SFB与消化道上皮细胞紧密相连，启动T细胞和B细胞的活化，促进平衡的免疫应答[82,84–85]。

辅助性T（Th）细胞是一种受肠道严格调控的效应T细胞。肠道微生物群的早期定植诱导免疫Th细胞亚群，如Th1、Th17和调节性T（Treg）细胞的分化和反应[80, 84]，对于维持肠道免疫稳态至关重要。例如，SFB的定植通过诱导血清淀粉样蛋白A（SAA，一种在肝脏中合成的急性期血浆蛋白）[86]和来自肠上皮细胞的活性氧（ROS，由来自肠上皮细胞的超氧化物和不完全还原产生的短暂亲电化学物质[87]）来促进Th17细胞的诱导[88]。成熟的Th17细胞通过分泌白介素（IL）-17、IL-17F和IL-22来保护宿主免受细菌感染，尤其在小肠固有层中[85]。除SFB外，*Clostridium*还可诱导叉头盒蛋白3（$Foxp3^+$）Treg细胞的发育[89]。*Clostridium*物种激活基质金属蛋白酶（MMP）的产生，MMP产生具有生物活性的转化生长因子-β（TGF-β），诱导$Foxp3^+$ Treg细胞的发育和维持[90]。$Foxp3^+$ Treg细胞被激活后可分泌IL-10 [91]。IL-10通过抑制IL-12和IL-23来抑制Th1和Th17的分化，进而驱动巨噬细胞发挥免疫耐受以维持免疫稳态[91]。

小肠Peyer斑块的生发中心可以通过SFB的附着来激活，从而促进B细胞的激活[92]。活化的B细胞（即浆细胞）可以通过血淋巴循环迁移回肠黏膜；然后循环浆细胞分泌免疫球蛋白A（IgA，黏膜表面产生的主要抗体同位素，协助肠道微生物群的发育和维持[93]）。此外，IgA分泌可以阻止SFB黏附于上皮细胞，从而抑制免疫激活[82]。

除了与宿主直接相互作用，共生微生物群还可以通过

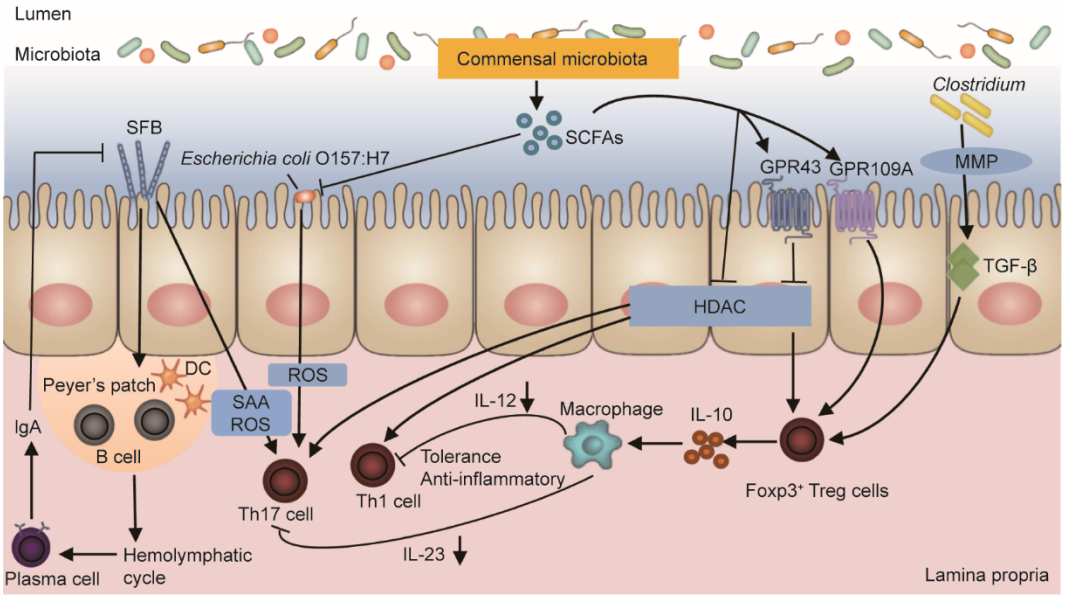

图 1. 肠道菌群在免疫发育和稳态维持中的作用。肠道微生物促进适应性免疫系统的发育和成熟，有助于宿主在抵抗外来病原侵袭和抗炎稳态之间取得平衡，建立一个平衡成熟的免疫系统。SFB：分段丝状细菌；GPR：G蛋白偶联受体；TGF-β：转化生长因子β；MMP：基质金属蛋白酶；DC：树突状细胞；SAA：血清淀粉样蛋白A；ROS：活性氧；HDAC组蛋白脱乙酰酶；IL：白细胞介素；Treg：调节性T细胞；Foxp3⁺：Foxp转录因子3；Th：辅助性T细胞。

肠道来源的代谢物，如SCFA（包括丁酸盐、乙酸盐和丙酸盐）调节免疫系统[94–95]。SCFA通过G蛋白偶联受体（GPR）促进肠道免疫的发育[80,90,96–97]。例如，醋酸盐通过抑制组蛋白脱乙酰酶（HDAC）活性触发Th1和Th17细胞的发育[98]。醋酸盐可以通过抑制*Escherichia coli* O157:H7志贺毒素的转运，诱导ROS产生，促进Th 17细胞的发育，保护宿主免受致命感染，从而维持肠上皮屏障的完整性[99]。此外，丁酸盐可以通过刺激GPR109A信号转导促进Foxp3⁺ Treg细胞分化。Foxp3⁺ Treg细胞的堆积及其抑制活性可以由丁酸盐和丙酸盐通过GPR43抑制HDAC活性来驱动[89–90]。因此，肠道微生物群促进适应性免疫系统的发育和成熟，并帮助宿主在抵抗外来病原体入侵和抗炎稳态之间取得平衡。

肠道来源的LPS是先天免疫系统发育的另一个重要因素。LPS被认为是宿主先天免疫系统最有效的刺激剂之一[100]。例如，研究人员已经证明LPS可能会影响肠道相关淋巴组织中Treg细胞的成熟[101–103]。此外，LPS可以通过Payer斑块腔表面上的微折叠细胞被运输到上皮下圆顶，然后被树突细胞采样并呈递给淋巴细胞，进而诱导产生IgA的B细胞的成熟[104–105]。此外，低内毒素LPS的优势可能会诱导和改变先天免疫系统的激活、诱导Treg细胞或阻止Th1/Th17反应，所有这些对于调节肠道免疫平衡至关重要[101]。因此，LPS对肠道免疫细胞至关重要。

4.2. 神经发育过程中的肠道微生物群和中枢神经系统

肠道微生物影响神经发育的能力使它们对人类发育产生了另一个重大影响。这些发现已通过幼龄无菌（GF）动物的行为和对其进行的认知评估得到证实[106]。众所周知，大脑的海马、纹状体和杏仁核区域与学习、记忆、运动和情绪有关（图2）。海马体主要负责记忆和空间导航。研究发现GF小鼠海马中低聚果糖（FOS）活性、5-羟色胺受体1A（5-HT_{1A}）水平和脑源性神经营养因子（BDNF）表达降低，导致其记忆和工作功能受损[107–108]。纹状体整合了运动和情绪反应，并与运动相关的基底神经节和边缘系统密切相关[109]。GF小鼠纹状体中多巴胺、血清素神经递质和突触囊泡蛋白（突触发生的间接标志物）增加会导致焦虑样行为[110]。此外，杏仁核（“情绪大脑”边缘系统的一部分）中*N*-甲基-*D*-天冬氨酸受体（NMDAR）、5-HT_1和BDNF水平的降低，以及GF小鼠纹状体的改变，导致冒险行为的增加[107,111]。

尽管已知微生物群-肠-脑轴涉及神经、激素和免疫信号传导，但对其确切机制（大脑和肠道通过该轴进行双向交流）尚未完全了解[112]。两种主要类型的神经细胞参与肠道微生物群和中枢神经系统之间的串扰[113–114]。这些神经细胞类型之一是小胶质细胞，该类细胞是中枢神经系统中最丰富的天然免疫细胞，占大脑神经胶质细胞的10%~15% [36]。小胶质细胞在生命早期参与中枢神经系统的发育，并在人的一生中参与抗原呈递、吞噬作用和炎症调节[115–116]。微生物代谢物包括SCFA、组胺和色氨

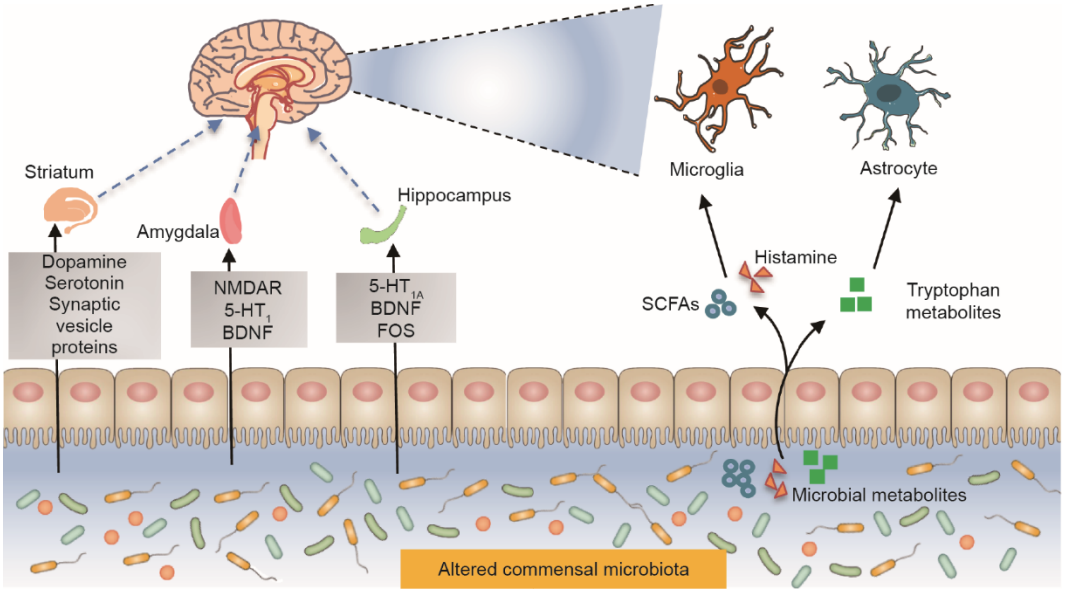

图 2. 神经发育过程中肠道微生物和中枢神经系统之间的神经免疫互作。NMDAR：NMDA 受体；5-HT：5-羟色胺；BDNF：脑源性神经营养因子；FOS：低聚果糖。

酸代谢物，是轴中必不可少的信使[97,117–119]。SCFA 在促进小胶质细胞成熟和维持正常生理功能方面发挥重要作用[40]。组胺是小胶质细胞的另一个重要发育信号，据报道组胺可以调节宿主行为和认知[120–121]。除了食物来源[122]，来自肠道的组胺分泌细菌还包括 *Escherichia coli*、*Lactobacillus vaginalis* 和 *Morganella morganii* [123]。微生物来源的组胺影响小胶质细胞的激活和分泌促炎因子，有助于神经发育过程中的免疫稳态[124]。

星形胶质细胞是一组具有多种功能的神经胶质细胞，是中枢神经系统中另一种重要的免疫细胞类型。除了在神经炎症中发挥重要作用外，星形胶质细胞还参与离子稳态、神经递质清除、糖原储存、血脑屏障的维持和神经信号转导[125]。肠腔中大多数未消化的膳食色氨酸转化为吲哚，然后通过微生物和肝酶进一步代谢或修饰，产生对芳烃受体（AhR）具有不同亲和力的吲哚衍生物[36]。来自膳食色氨酸的微生物代谢物可以激活 AhR 以减轻星形胶质细胞的炎症。此外，5-羟色胺（5-HT）（由 5-羟色氨酸形成的色氨酸衍生而来）是已知的在中枢神经系统发展过程中，用于调节神经元分化和迁移以及轴突生长、髓鞘形成和突触形成的关键神经递质[126–127]。研究还表明肠道微生物群 *Clostridial* 在调节源自肠嗜铬蛋白的 5-HT 水平方面发挥重要作用[118]。最近，研究发现自闭症谱系障碍（ASD）小鼠模型中肠道微生物群的改变与肠道 5-HT 的产生受损有关[128]。有趣的是，与正常饮食的小鼠相比，营养丰富饮食的小鼠微生物多样性显著提高；伴随着肠道微生物组的明显改变，营养丰富饮食的小鼠表现出改善的记忆、学习和焦虑行为[129]。这一证据表明，饮食引起的微生物群的短暂变化会影响行为，这是一个需要进一步研究的有吸引力的问题。

5. 从婴儿期到儿童期的肠道微生物群及其临床意义

了解婴儿期到儿童期健康肠道微生物群的特征，可为肠菌相关儿科疾病提供治疗新靶点，有利于早期发现易感人群，还可以促进形成预防和治疗这些疾病的新策略，包括干预生命早期即“窗口”期的微生物群[130]。许多研究表明，某些肠菌紊乱伴随儿科疾病甚至成年后疾病风险的增加。

5.1. 肥胖症

在过去的几十年中，大多数国家的超重和肥胖症儿童的患病率持续上升，被认为是一项重大的全球健康挑战[131]。最近的报道估计，2016 年有 4000 万 5 岁以下儿童以及超过 3.3 亿 5~19 岁儿童和青少年患肥胖症[132]。肥胖症通常始于儿童期或青春期，是许多主要慢性病（如 2 型糖尿病和冠心病）的最大危险因素之一[133]。有趣的是，儿童早期反复接触抗生素与较高的平均体重指数（BMI）和肥胖症倾向有关[75]。与人类基因组的遗传成分一样，人类微生物组在肥胖症的发展中也起着重要作用[6]。最近的一项发现表明，三岁超重儿童的胎粪微生物组（Bacteroidetes 比例更高）与正常体重儿童的胎粪微生物组不同

[134]。同一项研究表明，肠道微生物群（首过胎粪）与婴儿在怀孕和分娩期间超重存在关联。一项针对比利时儿童的研究表明，肥胖症儿童的Firmicutes/Bacteroidetes比例较高，*Lactobacillus*水平也较高，*Staphylococcus aureus*的比例分别与炎症标志物和能量摄入呈正相关[135]。此外，在生命的最初几个月，*Streptococci*和*Bifidobacterium*的定植可以预测BMI的变化，并且对BMI的影响取决于未来抗生素的使用[136]。值得注意的是，Stanislawski等[137]证实两岁婴儿的肠道微生物组分类和α多样性测量与晚年的BMI有很强的相关性，可以作为识别肥胖症高危儿童的指标。最近，在肥胖症儿童中发现了*Blautia*物种（尤其是*Blautia luti*和*Blautia wexlerae*）的消失，可能导致代谢炎症和胰岛素抵抗[138]。

肠道微生物群的改变可能通过SCFA等代谢物促进肥胖症的发展。SCFA是可以与回肠和结肠的肠内分泌L细胞以及脂肪细胞和免疫细胞中的GPR41和GPR43结合的配体[139–140]。SCFA在肥胖症发展中的作用是有争议的。研究表明，富含纤维的饮食与肥胖症和代谢综合征的发病率较低有关[141]。这可能是因为由可发酵膳食纤维转化而来的SCFA可以通过激活游离脂肪酸受体（FFAR）、促进肽YY（PYY）和胰高血糖素样肽-1（GLP-1），抑制食欲、增加饱腹感和预防肥胖症的发生[140]。然而，与此形成鲜明对比的是，其他研究表明，富含纤维的饮食实际上可能会促进而不是预防肥胖症的发展。例如，肥胖症儿童具有大量的Firmicutes/Bacteroidetes，这些细菌可促进SCFA与GPR41/GPR43的结合[142]；脂肪细胞中GPR的激活可触发肠道内分泌细胞中PYY的分泌[143]。反过来，PYY可以减慢肠道转运时间，提高能量摄取效率，并导致肥胖[144]。其他研究结果还表明，过量的SCFA会扰乱能量调节的平衡，同时可以与FFAR相互作用并参与胰腺β细胞葡萄糖刺激的胰岛素分泌和食欲控制肽激素的释放[145]。因此SCFA在肥胖症和相关疾病中的作用仍然是一个重要争论点。

革兰氏阴性菌产生的LPS是导致肥胖症的另一个重要因素[146]。在脂肪生成中，LPS参与免疫反应，介导免疫细胞的炎症和浸润，从而干扰肠道屏障和随后细菌或细菌产物的易位[142]。此外，肠道微生物组的改变会导致肝脏、心脏和肾脏中胆汁酸池的变化，进而影响法尼醇X受体核拮抗剂，导致肥胖症和胰岛素抵抗[147]。

5.2. 1型糖尿病

T1D是一种以胰岛β细胞为靶点的自身免疫性疾病[148]。随着时间的推移，TID已成为世界范围内一个主要的公共卫生问题[15]。根据国际糖尿病联盟（International Diabetes Federation）的数据，1 110 100名20岁以下儿童和青少年患有T1D，全球T1D总体年增长率约为3%[149]。已有研究表明，T1D与自身抗体相关，自出生后第一年就可以发现这种抗体，而年轻时患有T1D的患者病情更严重[150]。由于携带T1D相关人类白细胞抗原风险等位基因的个体的发生率仅为50%，因此非遗传因素在T1D的发展中很重要[7]。

最近的研究强调了肠道菌群在T1D中的作用。如Leiva-Gea等[151]发现肠道菌群，包括*Bacteroides*、*Ruminococcus*、*Veillonella*、*Blautia*和*Streptococcus*在T1D患者中富集，并且使脂质和氨基酸代谢、ATP结合盒转运、LPS生物合成相关的代谢基因表达、花生四烯酸代谢、抗原加工和呈递以及趋化因子信号通路得到增强。此外，Vatanen等[148]发现T1D患者中参与细菌发酵和SCFA生物合成的基因水平较低。他们还发现，健康儿童肠道中可能含有大量益生菌，如*Lactobacillus*，而T1D儿童的微生物群可能以*Lactobacillus*为主[148]。值得注意的是，肠道微生物代谢产物SCFA的减少与糖尿病易感性密切相关[152–153]。由于饮食、感染、药物等因素的影响，粪便SCFA，尤其是醋酸盐和丁酸盐的减少，导致胰岛Treg细胞减少，自身免疫T细胞增多，最终诱发T1D [154–155]。更具体地说，丁酸盐缺乏会减少肠上皮细胞的附着，增加肠道通透性，并增加细菌抗原暴露，从而诱导免疫反应，导致T1D的自身免疫[156]。除了SCFA外，在早期PAT治疗的小鼠中，还证明了一种使宿主易患T1D的微生物群，其特征是Bacteroidetes和Actinobacteria减少，*Proteobacteria*和*Akkermansia muciniphila*增加[76]。

5.3. 过敏性疾病——哮喘和食物过敏

哮喘是一种慢性炎症性疾病，影响全球超过3亿人[157]。食物过敏在婴幼儿中很常见[158]，儿童中的总体患病率为12% [130]。微生物群假说表明，肠道微生物群在过敏和哮喘等免疫疾病中将环境变化与免疫系统联系起来[159,32]。

多项研究检验了肠道微生物群与儿童过敏性疾病之间的关系。Zimmermann等[160]通过荟萃分析确定儿童过敏性疾病和哮喘的发生与Bacteroidaceae、Clostridiaceae和Enterobacteriaceae的富集，Bifidobacteriaceae和Lactobacillaceae的减少密切相关。另一项针对加拿大婴儿的研究发现，在3个月大的婴儿中，*Faecalibacterium*、*Lachnospira*、*Veillonella*和*Rothia*丰度低与过敏性疾病和哮喘的高风险相关[157]。同样，一项针对美国1~11个月大婴儿进行监

测的纵向研究表明，*Faecalibacterium*、*Lachnospira*、*Veillonella*和*Rothia*丰度较低的一个月大婴儿在4岁时哮喘发病率较高[161]。此外，在使用大环内酯类药物进行治疗的婴儿中发现了微生物群的长期改变，这与哮喘风险增加和抗生素相关体重增加的倾向有关。这一发现强调了生命早期肠道微生物组对健康的贡献[77]。此外，微生物代谢物，如高浓度的12,13-diHOME会影响过敏性疾病的发生率[162]。

牛奶过敏（CMA）是婴儿期最常见的过敏现象，影响全球2%~3%的婴儿[163]。研究表明，CMA与肠道微生物群之间存在密切关系。例如，Canani等[164]发现CMA婴儿肠道菌群的多样化，其主要特征是Lachnospiraceae和Ruminococcaceae的富集，*Bifidobacterium*和*Escherichia*的减少。Bunyavanich等[165]还对牛奶过敏婴儿进行了纵向研究，他们分析了3~16个月大婴儿的粪便样本，然后在几个时间点（在入学时、6个月、12个月，然后每年一次，直到8岁）进行了临床评估、牛奶特异性IgE水平和牛奶皮肤点刺试验。有趣的是，富含*Clostridium*和Firmicutes的婴儿与牛奶过敏症状有关，这些症状在他们8岁时消退。值得注意的是，虽然大多数儿童早期食物过敏症状会在儿童后期自我修复，但对某些过敏原（如花生或坚果）的敏感性可能会持续到成年[130]。

根据不同的潜在病理生理学特性，食物不良反应可分为食物不耐受（非免疫介导）和食物敏感（免疫介导）[166]。除了免疫机制，现有研究已将食物过敏与由肠道感染或共生肠道微生物群的变化引起的各种微生物信号联系起来[167–168]。例如，*Bifidobacterium*通过产生醋酸盐促进肠上皮完整性并防止致命感染，然后通过诱导肥大细胞凋亡缓解食物过敏[99]。此外，SCFA或色氨酸衍生代谢物可以直接调节黏膜免疫功能和肠道屏障完整性，从而影响身体对食物的敏感性[169–170]。此外，丁酸盐通过调节转录因子Foxp3$^+$ Treg细胞的比例和功能来调节宿主对食物抗原或过敏原的耐受性[171–172]。有趣的是，丁酸盐的存在会导致食物过敏，而细菌代谢物的缺乏可能会损害肠道稳态，进而导致宿主容易发生食物过敏[173]。

5.4. 发育迟缓

发育迟缓是一种严重的生长障碍疾病，影响全球1.55亿5岁以下儿童[174]。发育迟缓与反复腹泻感染、卫生条件差和营养缺乏有关，其中营养缺乏又与肠道微生物群的改变有关[175]。重要的是，发育迟缓的儿童的*Escherichia coli*/*Shigella* sp.、*Campylobacter* sp.、Proteobacteria相对丰富，但Clostridia减少[45,176]。在对印度南部儿童的另一项研究中发现，发育迟缓的儿童富含Bacteroidetes、Campylobacterales和*Desulfovibrio* [177]。

发育迟缓可能是由环境肠道功能障碍（EED）[178–179]导致的，此外还被猜测是由以口咽物种为特征的小肠细菌的过度生长所导致；因为这种过度生长会导致局部炎症，从而引起肠道吸收和消化功能受损[177]。发育迟缓中肠道微生物群的紊乱与免疫反应[180–181]和肠道通透性[180,182–183]的变化有关。具有特定生物学和功能的微生物产品可能会影响儿童对EED的敏感性。例如，研究发现，在赞比亚儿童中，*Citrobacter rodentium*可降低两种EED症状，即肠绒毛高度和增加的肠道通透性[184]。发育迟缓儿童体内的微生物群可以减少一些代谢途径，如氨基酸、碳水化合物利用和B族维生素代谢，从而导致EED [185]。

5.5. 自闭症谱系障碍

ASD是一种神经发育障碍，发生在出生后的前三年，其特征是社交沟通障碍、狭窄和有限的兴趣以及重复行为[186]。ASD影响美国2.24%的儿童[187]，而中国ASD的患病率为每10 000名儿童中有11.8人[188]。除了认知方面，胃肠道疾病是ASD儿童常见的非神经系统症状[189]。

在一项关于中国ASD儿童的研究中，发现Bacteroidetes/Firmicutes的比例丰富，*Sutterella*、*Odoribacter*和*Butyricimonas*的相对丰度，以及*Veillonella*和*Streptococcus*减少[190]。此外，某些肠道微生物群可能参与ASD的发病机制。例如，与健康对照组相比，在患有胃肠道障碍的ASD儿童的胃肠道活检中发现了高致病率的*Sutterella*物种[191]。此外，Sandler等[192]发现在口服6周抗生素万古霉素（万古霉素是一种针对Clostridia的抗生素）治疗ASD的10名儿童中，其中8名儿童的神经行为症状和胃肠道症状得到显著改善。这些研究有力地表明*Sutterella*和Clostridia等细菌在自闭症的发病机制中发挥作用。

微生物群也可能参与ASD的免疫和炎症反应。例如，已经报道了在ASD中小胶质细胞的失调[193]，其体内平衡、成熟和功能受到肠道微生物群（如*Bacteroides distasonis*、*Lactobacillus salivarius*和*Clostridium cluster XIV*）的影响[40]。此外，微生物代谢产物SCFA可以通过抑制HDAC来抑制单核细胞、巨噬细胞和树突细胞的成熟，然后改变这些细胞捕获抗原的能力并减少促炎细胞因子的产生[194]。SCFA还可以调节肠道激素（包括PYY、GLP-1、胰岛素、生长素释放肽和瘦素）的分泌，所有这些都已被证明与ASD相关[195]。

ASD儿童肠道微环境中芳香族物质、谷氨酸代谢和胆汁酸代谢的变化也极为重要。例如，在ASD小鼠模型中，肠道*Bifidobacterium*和*Blautia*的减少与胆汁酸和色氨酸代谢缺乏以及社交互动受损有关[128]。此外，Wang等[187]发现ASD患者谷氨酸代谢的变化与低水平的*Bacteroides vulgatus*以及高水平的有害*Eggerthella lenta*和*Clostridium botulinum*有关。学者还发现，减少的肠道2-酮基谷氨酸是ASD的潜在生物标志物，与肠道激素11-脱氧人前列腺素F（PGF2）直接相关，并影响神经递质谷氨酸抑制/兴奋性失衡[187]。

5.6. 炎症性肠病

近年来，儿科IBD的全球发病率一直在上升[196]。在美国和加拿大，IBD的发病率约为每100 000名儿童中有10例，并且还在继续上升[196–197]。在儿科IBD病例中，4%出现在5岁之前，18%出现在10岁之前，并在青春期达到高峰[197]。IBD包括克罗恩病（CD）和溃疡性结肠炎（UC），通常始于儿童期或青春期；IBD以慢性肠道炎症为特征，由遗传决定因素的复杂相互作用、黏膜屏障破坏、异常炎症信号、耐受性丧失和环境触发因素引起[198–199]。

在环境危险因素中，肠道菌群在小儿IBD的发病机制中起着重要作用。患儿科IBD儿童的微生物多样性显著降低[200]。在UC中，肠道中已知阳性细菌（如*Eubacterium rectale*、*Faecalibacterium prausnitzii*）的丰度显著减少，而已知病原体（如*Escherichia coli*）则富集[200]。CD与α多样性降低有关；Enterobacteriaceae、Pasteurellaceae、Veillonellaceae、Fusobacteriaceae的丰度增加；以及Erysipelotrichales、Bacteroidales、Clostridiales丰度减少[201]。另一项使用宏蛋白质组学的研究报道了儿科IBD中增加的4种门：Proteobacteria、Verrucomicrobia、Ascomycota和Spirochetes [202]。与儿科IBD明显相关的属是减少的*Bacteroides*和增加的*Faecalibacterium* [202]。

肠道来源的代谢物也参与儿科IBD的发展[200,203–206]。例如，小儿IBD中产SCFA细菌的数量和丁酸盐的浓度已被证明减少，这与肠黏膜中促炎免疫细胞数量显著增加有关，甚至与IBD的表现和严重程度相关[203]。

6. 微生态干预——益生菌/益生元和粪便菌群移植

6.1. 益生菌/益生元——儿科疾病的治疗和安全问题

通过提供益生菌或益生元干预肠道微生物群，可以有效改善与代谢、过敏和自身免疫疾病相关的儿科疾病症状[206–209]。益生菌和益生元是有益于宿主健康的微生物群管理工具。益生菌的共识定义是“活的微生物，当给予足够量时，赋予宿主健康益处”，而益生元的定义是“宿主微生物选择性利用的底物，赋予健康益处”[24, 210–211]。

多项研究调查了益生元对儿科疾病的影响。Nicolucci等[206]观察到菊粉治疗显著降低了肥胖症儿童的身体脂肪和躯干脂肪，并与*Bifidobacterium*增加和*Bacteroides vulgatus*减少有关。在小鼠模型中，长链菊粉被证明能通过调节肠道-胰腺免疫、屏障功能和微生物稳态来抑制T1D [21]。此外，益生元Bimuno®低聚半乳糖被用于治疗自闭症儿童6周后，自闭症儿童的胃肠功能和反社会行为得到改善，Lachnospiraceae显著增加，粪便和尿液代谢物发生明显变化[207]。最近的一项研究发现，ASD儿童服用4种益生菌菌株（*Bifidobacterium infantis* Bi-26、*Lactobacillus rhamnosus* HN001、*Bifidobacterium lactis* BL-04和*Lactobacillus paracasei* LPC-37）与FOS的混合益生菌后，自闭症和胃肠道症状的严重程度得到显著缓解[212]。当给予*Lactobacillus acidophilus*益生菌补充剂时，发育迟缓的印度儿童的体重、身高和发病率，以及腹泻、发烧、咳嗽和感冒症状均有所改善[213]。

尽管存在争议，但益生菌对自身免疫性疾病的疗效仍是一个热门话题。例如，Savilahti等[208]为孕妇（夫妇双方其中一方或双方有医生诊断的过敏症）从第36个妊娠周到分娩提供混合益生菌胶囊，其中包括*Lactobacillus* GG（ATCC 53103）、*Lactobacillus rhamnosus* LC705（DSM 7061）、*Bifidobacterium breve* Bb99（DSM, 13692）、*Propionibacterium freudenreichii* ssp. *shermanii* JS（DSM 7076）。婴儿被给予相同的胶囊6个月，并在2岁、3岁和15岁时接受随访。然而，益生菌治疗对自身免疫性疾病的发生没有影响[208]。相比之下，Huang等[23]评估了*Lactobacillus paracasei*（LP）、*Lactobacillus fermentum*（LF）及其组合（LP + LF）对儿童哮喘的影响，发现益生菌干预有效降低了哮喘的严重程度，LP + LF的组合似乎比单独使用LP或LF更有效。此外，Buffington等[209]表明益生菌*Lactobacillus reuteri*纠正母体高脂肪饮食诱导的肥胖症小鼠大脑腹侧被盖区的催产素水平和突触功能障碍，并选择性地逆转社会缺陷——与后代神经发育障碍相关的特定行为异常肥胖小鼠。

败血症的发生是补充益生菌的风险之一，尤其在新生儿和孕妇中[214]。例如，*Lactobacillus rhamnosus* GG引起的败血症在婴儿中已有报道，包括右心室和肺动脉双出

口狭窄修复术后并发症一例、短肠综合征两例[215–216]。也有报道称婴儿服用 *Lactobacillus* 后过敏反应增加[217–219]。至于有害的代谢活动，从在重症监护中使用益生菌的儿童中观察到感染并发症的增加趋势[220]。其他代谢问题包括益生菌产生的 *D*-乳酸的影响和胆汁盐的解偶联[221]。尽管理论上可以在肠道或其他地方的益生菌生物体和其他生物体之间进行横向基因转移，但迄今为止尚未报道有关抗生素耐药性转移的临床证据[214,222]。为了提高益生菌干预的安全性，迫切需要研究益生菌活性的潜在机制。益生菌的理论风险也必须根据所用微生物的特性进行评估。此外，应合理利用微生物群落和相关动物模型设计的类器官，以更好地探索益生菌的作用机制。

6.2. 粪便微生物群移植——儿科疾病的治疗和安全问题

粪便微生物群移植（FMT）是一种耐受性良好、简单且有前景的儿科疾病治疗方法。FMT 已用于治疗儿科疾病，如 ASD [223]、IBD [224]、*Clostridium difficile* 感染[225]和难治性腹泻[226]。与成人的研究结果一致，患 *Clostridium difficile* 感染的两岁儿童的症状通过 FMT 得到缓解，并且在随访的 6 个月内没有复发[225]。FMT 也缓解了两名顽固性腹泻儿童的病情[226]。有趣的是，在给予初始高剂量 FMT 和每日低剂量维持 7~8 周后，7~16 岁 ASD 儿童的胃肠道症状减少了约 80%，这种改善维持了 8 周[223]。在 IBD 中也发现 FMT 的积极作用：对 10~17 岁儿童进行两周 FMT 治疗，可改善 UC 和 CD 结肠炎评分，而相关的副作用是自限性和良性的[224]。在最近一项关于母亲 FMT 的研究中，7 名剖腹产婴儿接受了母亲的 FMT；母亲的微生物组成逐渐显示出与阴道分娩婴儿微生物组成的相似性[227]。本研究表明，母亲产后 FMT 可以恢复剖腹产婴儿的微生物群落，为预防儿科疾病提供新的方向。最近，剖腹产出生的 30 名婴儿口服接种了母体阴道细菌样本，而相关测试结果尚未公布[228]。然而，一些研究报道了不良反应[229]。因此，应建立标准协议以保持 FMT 安全。

7. 婴幼儿肠道菌群的结论与展望

肠道菌群与人类的生长发育密切相关。人类生命前三年微生物群的定植和菌群是微生物群建立以及可能的医学干预的极其重要的“窗口”阶段。然而，需要阐明肠道微生物群的动态变化及其与婴幼儿疾病的因果关系，以促进高度专业化的治疗。尽管现有的研究结果是基于大样本的长期随访研究，但由于肠道微生态的影响因素较多，这些研究的效果受到其单因素样本分组设计的限制，因此未来的研究需要多因素样本分组设计。

除了本文讨论的肠道细菌外，肠道病毒和真菌也是人类肠道群落的重要组成部分[230–231]。一项研究显示，1~4 个月大的人类婴儿的肠道真菌主要为 Saccharomycetales 和 Malasseziales；真菌最终在 5~11 个月内成熟，直到 Malasseziales 减少，而 Saccharomycetales 保留下来[161]。最近的研究表明，肠道真菌会导致 ASD [232]、哮喘[233]、过敏性疾病[234]、肥胖症[235]和 T1D [236]。一些研究提供了初步证据，表明真核病毒具有促进肠道稳态和塑造黏膜免疫的能力[237]。例如，某些肠道病毒可以在体外感染 β 细胞，并已在 T1D 患者的胰岛中检测到该病毒，其机制与 T1D 相关[238–240]。

最近，关于胎盘中是否存在微生物群以及胎盘微生物群在婴儿出生后早期生命微生物组形成中的作用等问题引起了广泛的讨论。早期研究报道称，健康足月分娩期间胎盘的微生物群富含 *Lactobacillus* sp.、*Propionibacterium* sp. 和 Enterobacteriaceae [241]。另一项研究发现，在无菌剖腹产期间收集的胎盘具有 Proteobacteria 的特征[242]。有趣的是，口腔细菌被认为是胎盘细菌的主要来源[243]，并在动物实验中得到证明[244–245]。然而，最近的研究发现，没有足够的证据支持胎盘样本中存在细菌。De Goffau 等[246]发现几乎所有 16S rRNA 基因扩增子测序中的信号都与分娩过程中细菌的获得或实验室试剂中细菌 DNA 的污染有关，而不是将胎盘本身作为其来源；唯一的例外是 *Streptococcus agalactiae*（B 组 *Streptococcus*）。此外，在分娩开始前收集的样本中约有 5% 未检测到污染信号。同样地，从足月分娩或自然早产的胎盘中也无法检测到细菌的存在[247]。尽管如此，胎盘中是否有细菌仍然未知，因此需要对母亲和后代进行后续观察。

研究表明，对肠道微生物群的干预可以改善儿科疾病，包括肥胖症、T1D、过敏性疾病、ASD 和发育迟缓。首先，益生菌和益生元干预对这些疾病显示出有希望的效果（图 3）。还有其他微生态干预措施，如后生元[248]、噬菌体治疗[249]、FMT [223]和营养干预[250]。在开发新的有效微生态制剂时，可以使用数学模型产生和提出创新想法，以促进有效益生菌和人工 FMT 菌株的开发[251]。

在开发益生菌制剂时，必须注意安全性和持久性问题，因为之前的研究已经发表了有争议的结果[23,208–209]。这些争议可能是由特定微生态制剂、剂量、临床终点或目标人群的差异所致[24]。此外，对评估益生菌、益生元或合生元的 384 项随机对照试验的系统评价表明，这些研究往往缺乏对副作用的讨论，这可能导致开错药，并

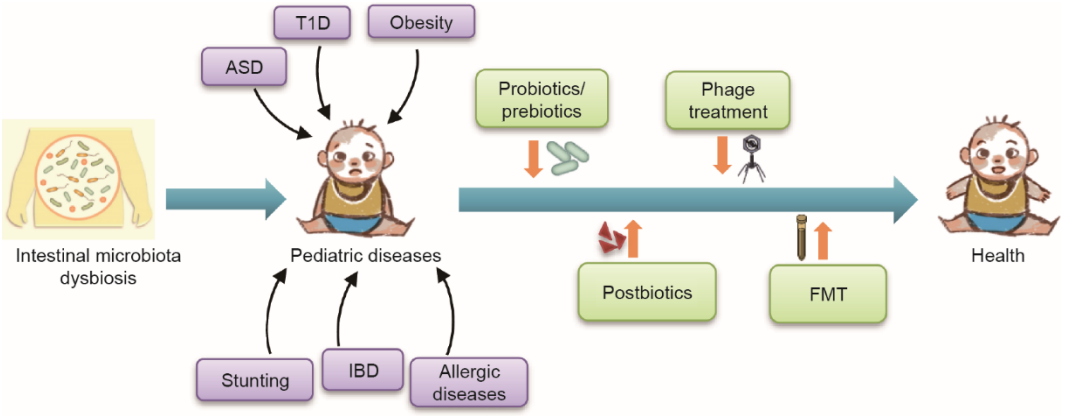

图 3. 基于肠道微生物群的儿科疾病治疗方法。最近的研究证明肠道微生态的调节可改善儿科疾病，如肥胖、I型糖尿病、自闭症、炎性肠病、过敏性疾病和发育迟缓。肠道调节的方法包括益生菌、益生元、后生元、噬菌体、菌群移植等干预手段。

使受试者随后出现不良反应[252]。此外，大多数单菌株益生菌并不能永久改变肠道群落，其有效性只有在反复使用的情况下才能持续[253]。重要的是，益生菌的理论风险包括全身感染、有害代谢活动、易感个体的过度免疫刺激、基因转移和胃肠道副作用，这些风险已在病例报告、临床试验结果和实验研究中得到体现[214,221]。因此，迫切需要确定益生菌制剂的适当成分。

肠道菌群与疾病之间的因果关系仍有待阐明；因此，必须花费时间和精力来阐明这些相互作用机制。此外，在临床应用中，应考虑个体差异，以实现个体化的微生态干预治疗。随着新一代测序技术[254]、多组学分析（即基因组学、元转录组学、宏蛋白质组学和代谢组学）[255]和组学（即培养组学）[256]的发展，肠道微生物群和疾病间的关系正日益被人们所认识。同时，出现了新的微生物组技术，如微生物生态系统（被称为EcoFAB）。这是一种透明的微生物生态系统模型，也是一种芯片肠道，即具备肠上皮细胞，液体在细胞周围流动，以及具有模拟肠道蠕动的能力[257]。这些技术将有助于未来对复杂微生物组机制的研究。进一步的研究应侧重于生命早期微生物对病理生理学、并发症和生活质量等复杂性的贡献，并应旨在改善与儿科疾病相关的长期结局。

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Compliance with ethics guidelines

Hanying Lv, Lijiang Zhang, Yuqiu Han, Li Wu, and Baohong Wang declare that they have no conflict of interest or financial conflicts to disclose.

Authors' contributions

B. Wang, H. Lv, L. Zhang, Y. Han, and L. Wu wrote the manuscript; B. Wang revised the manuscript.

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