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评 述

肠道菌群与宿主关系解析及肠道菌群调控/合成研究进展

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摘要 肠道菌群和宿主健康之间有着密切的关系, 其与宿主之间存在着复杂的相互作用, 如菌群及其代谢产物与免疫系统的互作、脑-肠轴、肺-肠轴等. 肠道菌群紊乱与多种疾病的发生和发展存在相关性, 且部分微生物菌株与一些疾病的发生存在着因果关系. 肠道菌群还会影响药物代谢, 个体差异的肠道菌群使得不同个体对于同种药物的代谢具有很大差别; 解析个体肠道菌群的状态及其与宿主之间的关系是实施个性化精准诊疗的重要环节. 肠道菌群具有可塑性, 通过饮食调控、益生菌/益生元/合生元补充、粪菌移植等干预手段可以使肠道菌群处于健康状态, 应用肠道菌群编辑和合成肠道微生物组等新技术调控、合成肠道菌群的研究已有报道. 目前, 利用合成生物学等方法调控肠道菌群已成为改善和治疗疾病的有效方法之一. 本文综述了肠道菌群与人体等宿主的相互作用、肠道菌群与部分疾病的相关性和因果性, 以及通过肠道菌群调控改善人体健康状态的策略, 展望了微生物组学和合成生物学在肠道菌群调控与合成方面的应用.

关键词 肠道菌群, 宿主-菌群互作, 短链脂肪酸, 菌群调控, 微生物组学, 合成生物学

肠道是微生物和人体等宿主之间相互作用的主要场所. 人体肠道细菌数量庞大, 与人体细胞数量相当, 细菌基因总数可达人类基因数量的100倍[1]. 肠道菌群以各种形式参与人体等宿主的生理活动, 与宿主的健康状态密切相关. 健康宿主与微生物之间存在着相互作用, 保持着一种互惠互利的平衡状态. 当肠道菌群发生紊乱时, 这种平衡的状态便会被打破, 导致各种疾病的发生和发展. 肠道菌群的失调表现为潜在致病菌的增长和有益菌数量的减少, 这种失衡状态和代谢性疾病、免疫疾病、精神类疾病等许多疾病都存在关联. 尽管肠道菌群具有稳定性, 但它也具备可塑性, 其组成会随着宿主的年龄、饮食、生活方式和环境暴露而变化[2]. 对肠道菌群及其与宿主相互作用的解析有利于疾病的诊断、治疗和预防, 特别是有助于个体化

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精准医疗的实施.

1 肠道菌群与人体等宿主的健康互作

1.1 肠道菌群的建立及其影响因素

新生儿出生之后，会直接接触来自母体以及周围环境中的微生物，同时这些微生物快速地在婴儿体内定植. 此后在整个生命周期中，人体与微生物之间不断发生着各种相互作用，保持着一种互惠互利的关系(图1). 阴道分娩的婴儿获得的菌群类似于母亲的阴道菌群, 以乳酸菌、普氏菌等为主[3]; 剖腹产婴儿失去了接受母体菌群的机会，接受了大量来自医院环境的条件致病菌，如粪肠杆菌、肺炎克雷伯菌等[4]. 研究表明，让剖腹产的婴儿在分娩后接触产妇阴道液体，有助于剖腹产婴儿建立健康的肠道菌群[5]. 婴儿出生后，抗生素治疗、喂养方式或环境暴露等因素会进一步影响婴儿的肠道微生物组和免疫系统[6]. 儿童时期肠道菌群稳态和儿童的健康状态关系密切，肠道菌群紊乱与一些疾病的发生密切相关，如营养不良[7]、哮喘[8]、过敏反应[9]等.

肠道微生物组存在着巨大的个体化差异. 根据肠道菌群的优势物种可以将其划分为三个特征型，称为肠型[10]，这三种肠型分别以拟杆菌属(*Bacteroides*)、普氏菌属(*Prevotella*)和瘤胃球菌属(*Ruminococcus*)为主. 肠型与人体健康状态存在着密切关联, 能够为个体化的精准诊断和治疗提供参考. 肠道菌群与遗传、年龄、性别等具有很强的相关性[2]，肠道微生态系统会随着宿主年龄增长发生演变: 幼儿期微生物群落结构变化迅速，成年期微生物群落结构趋于稳定，老年期微生物群落结构趋于紊乱[11]. 个体内部不同部位的菌群组成也存在差异，其中结肠细菌的密度高于胃和十二指肠[12]; 肠道菌群以来源于厚壁菌门(Firmicutes)、拟杆菌门(Bacteroidetes)、放线菌门(Actinobacteria)的细菌为主. 尽管肠道菌群在宿主成年后会保持相对稳

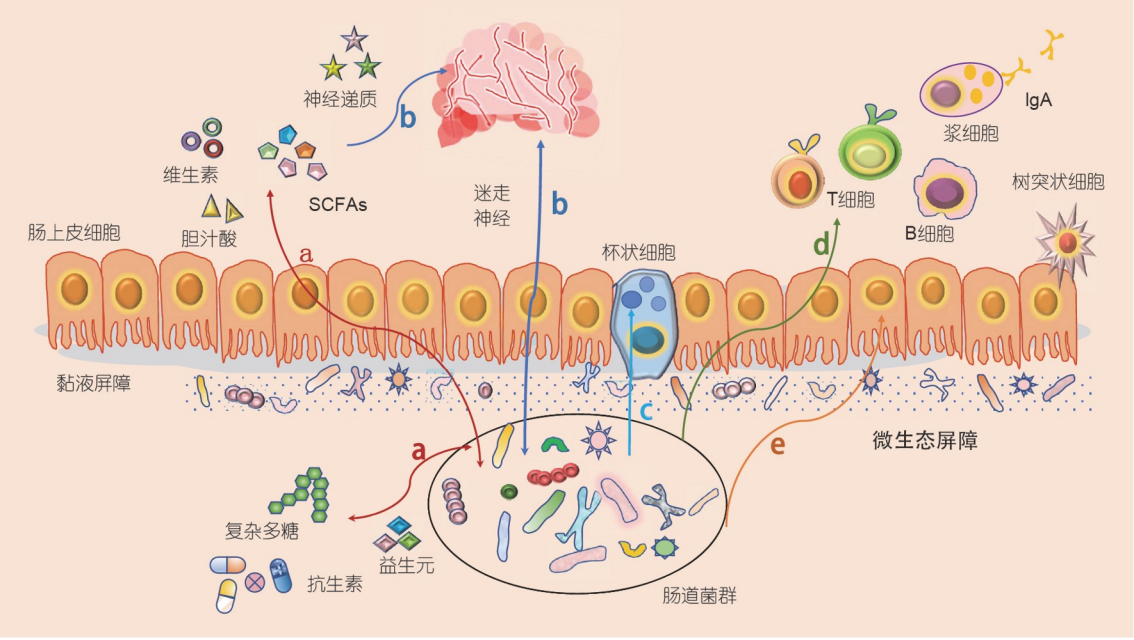

图 1 肠道菌群与人体的相互作用. (a)肠道菌群代谢复杂多糖等产生多种影响菌群结构和功能的生物活性物质，如短链脂肪酸、胆汁酸等; (b)肠道菌群及其代谢产物通过迷走神经影响大脑生理活动; (c)肠道菌群促进杯状细胞分泌黏蛋白，维持黏液层屏障的完整; (d)肠道菌群及其代谢物促进免疫系统的发育和成熟; (e)肠道菌群调节肠上皮细胞周期，改善肠上皮屏障的结构和功能(网络版彩图)

Figure 1 The interactions between gut microbiota and human body. (a) The gut microbiota metabolizes complex polysaccharides and produces a variety of bioactive substances, such as short-chain fatty acids and bile acids, which affect the structure and function of the gut microbiota; (b) the gut microbiota and its metabolites influence the physiological activity of the brain through the vagus nerve; (c) the gut microbiota promotes goblet cells to secrete mucin and maintains the integrity of the mucus barrier; (d) the gut microbiota and its metabolites promote the development and maturation of the immune system; (e) the gut microbiota regulates the intestinal epithelial cell cycle and improves the structure and function of the intestinal epithelial barrier (color online)

定的状态, 但它也具有较大的可塑性, 其组成会随着宿主的饮食结构[13]、生活方式、抗生素使用[14]等因素发生变化. 其中, 抗生素使用是导致菌群失调最直接的原因之一[15], 抗生素除了具有杀灭病原菌的作用, 还会降低宿主原生菌群的多样性、丰度和均匀性等特征[16]. 研究表明, 对幼年小鼠使用抗生素能够显著改变免疫细胞的数量和基因表达, 增加多种疾病的易感性[17].

1.2　肠道菌群及其代谢产物与宿主的相互作用

肠道菌群被认为是一个代谢器官, 其代谢能力超过了胃肠道、口腔和肝脏[18]. 菌群的代谢功能不仅有助于宿主从食物中获取营养和能量, 而且还可以合成和释放大量代谢物, 如短链脂肪酸、次生胆汁酸、胆碱代谢物和脂类物质等; 这些代谢物也具备丰富的生理功能, 它们可以进入宿主代谢循环并在肠道外发挥一系列作用, 并可通过它们对应的受体信号来调节宿主的代谢[19].

肠道自身无法消化复杂多糖等物质, 肠道菌群是消化这些物质的主力. 肠道菌群消化的同时, 会代谢产生乙酸、丁酸、乳酸和丙酸等短链脂肪酸(short-chain fatty acids, SCFAs); 这些短链脂肪酸对宿主肠道及人体其他器官均能发挥调节作用. 短链脂肪酸是一系列G蛋白偶联受体(G-protein coupled receptors, GPCRs)的配体, 这些受体表达于肠上皮细胞、脂肪组织和免疫细胞[20], 它们通过激活G蛋白偶联受体等机制激活并调节免疫细胞, 还可以促进肠道稳态的维持[21,22]. 短链脂肪酸还有助于调节肠上皮细胞周期和肠道通透性[23]; 丁酸盐是结肠上皮细胞的能量来源, 在低剂量时可以改善肠道屏障功能[24], 丁酸与(小鼠)胰岛素敏感性的调节也有关系[25]; 而丙酸和乙酸盐则是肝脏代谢的能量底物之一. 短链脂肪酸还具有调节多种脑活动相关代谢的作用[26].

胆汁酸是由肝脏胆固醇合成的内源性分子[27], 与肠道菌群之间存在着双向的相互作用. 肠道菌群可以调控胆汁酸合成中多种限速酶的表达[28]; 胆汁酸也可以通过促进胆汁酸代谢, 从而抑制胆汁酸敏感细菌的生长, 塑造并改变肠道菌群. 高脂肪饮食小鼠的厚壁菌门相对丰度增加, 而拟杆菌门相对丰度减少, 其原因可能是初级胆汁酸转化为次级胆汁酸的比例相对减少[29]. 肠道菌群可以通过胆汁酸修饰利用FXR和TGR5依赖的胆汁酸受体来调节信号传递[29], 根据肠道菌群、胆汁酸和FXR/TGR5信号通路之间的相互作用, 肠道菌群重塑有望成为治疗代谢性疾病的一种有效途径. 除了短链脂肪酸和胆汁酸, 肠道菌群还会产生大量可能影响宿主代谢的物质, 如细菌代谢物氧化三甲胺(trialkyphospline oxide, TMAO)与人类心血管疾病的发病相关[30]. 此外, 肠道菌群还可以为宿主提供叶酸、维生素K、生物素、核黄素(B2)、钴胺素(B12)等多种营养物质, 促进宿主健康[31].

1.3　肠道菌群与宿主免疫系统

胃肠道是人体最大的免疫器官, 其常驻微生物群是免疫系统的主要调节因子[32], 在免疫系统发育和成熟中起着非常重要的作用; 而肠道免疫细胞也能够直接或间接地通过免疫反应调节肠道菌群. 免疫系统不仅能抵御病原体, 还能够耐受与宿主共生的有益菌群[33], 许多共生菌被宿主肠道接受为“延伸的自我”[34].

微生物群的定植不仅有助于新生儿先天和适应性免疫的发展[35], 还会影响宿主生命后期的炎症调节[33]. 特定的细菌类群可以调节小鼠肠道的免疫反应, 如Th17、Treg或Th1和B细胞的激活等[36]. Th17细胞是由肠道分节丝状菌(segmented filamentous bacteria, SFB)诱导的; 某些梭状芽孢杆菌能够诱导调节性T细胞(regulatory T cell, Treg)亚群, 从而促进免疫耐受, 保护机体免受炎症和过敏性疾病的侵袭[37]. 粪杆菌(*Faecalibacterium prausnitzii*)、瘤胃球菌和嗜黏蛋白艾克曼氏菌(*Akkermansia muciniphila*, Akk)是与免疫细胞联系最紧密的类群, 会显著影响免疫系统稳态[38]. 但并不是所有的微生物都能促进宿主免疫系统健康, 一些机会致病菌可能会激活免疫系统, 引发炎症性疾病[39]. 除了共生菌的直接调节作用, 菌群的代谢物也可以影响肠道黏膜免疫系统[40], 如丁酸能够诱导功能性结肠Treg细胞, 特别是$CD4^+$ T细胞亚群, 进而通过T细胞内源性表观遗传上调Foxp3基因的表达[41]. B细胞发育、IgA的储备选择也是由肠道菌群调控的[42]. 肠道菌群可以促进先天髓细胞和淋巴细胞之间的相互作用, 从而有助于肠道免疫系统稳态[43]. 肠道菌群能够激发杯状细胞分泌黏蛋白, 保障黏液层结构的完整性, 发挥屏障作用[44]. 肠道菌群还可以调节肠上皮细胞的生长和发育(图1), 改善肠上皮屏障的结构和功能, 帮助宿主抵御病原体; 在小鼠模型中, 益生菌的定植可

以改善肠道的屏障功能, 促进宿主健康[45,46]. 肠道上皮细胞也可以通过释放microRNAs, 调控细菌的基因表达, 影响肠道菌群稳定[47].

1.4 肠道菌群与脑-肠轴

脑-肠轴是指由胃肠道、肠神经系统和大脑组成的网络, 即大脑和肠道之间存在的双向交流网络(图2). 这些双向通信可以调节免疫、消化、新陈代谢、饱腹感和应激反应等重要的生理功能, 而肠道菌群在其中承担着重要的作用. 肠神经系统与中枢神经系统间的沟通主要是由迷走神经介导的, 所以迷走神经在脑-肠轴的功能中发挥着重要的作用[48]. 无菌小鼠的研究模型表明, 发育、髓鞘形成、神经发生和小胶质细胞激活、血脑屏障调节等一些基本的神经过程主要依赖于肠道菌群的调控[49~51].

肠道菌群对神经炎症的调节起重要作用[52,53]. 肠道菌群产生的色氨酸衍生AHR配体可到达中枢神经系统, 具有调节星形胶质细胞功能、抑制炎症和神经变性的作用[54]. 肠道菌群的代谢物, 如神经递质、短链脂肪酸等能够参与神经激活, 调节肠神经系统近端神经元的突触活性, 与许多精神类疾病存在关联(图2). 短链脂肪酸通过肠道进入循环系统, 可通过刺激下丘脑-垂体-肾上腺(hypothalamic-pituitary-adrenal, HPA)轴影响神经系统的健康状态[55], 其中丁酸钠还具有抗抑郁的作用, 可以促进5-羟色胺的神经传递[56].

1.5 肠道菌群与肺-肠轴

随着细菌高通量培养技术的改善和二代测序技术的发展, 近期研究证实肺部存在着多样性丰富的微生物[57,58], 呼吸道的微生物群落对维持人类健康至关重要[59]. 许多呼吸道疾病患者合并有胃肠道症状; Nobel等人[60]的研究表明, 35%的新冠肺炎患者具有胃肠道症状. 肺肠之间存在着免疫系统介导的双向交流通路; 肠道菌群的多种代谢产物(如短链脂肪酸[61]、去氨基酪氨酸[62]等)会影响肺部的免疫反应; 免疫细胞甚至能够从肠道迁移至呼吸道[63], 从而帮助宿主抵御呼吸道病原菌的侵袭. 多个研究表明, 为呼吸道病毒感染的动物补充乳酸菌[64]、双歧杆菌[65]、鼠李糖杆菌[66]等益生菌可以显著促进呼吸道疾病的治疗. 鼻内接种益生菌, 以及粪菌移植、后生元补充等干预肠道菌群的

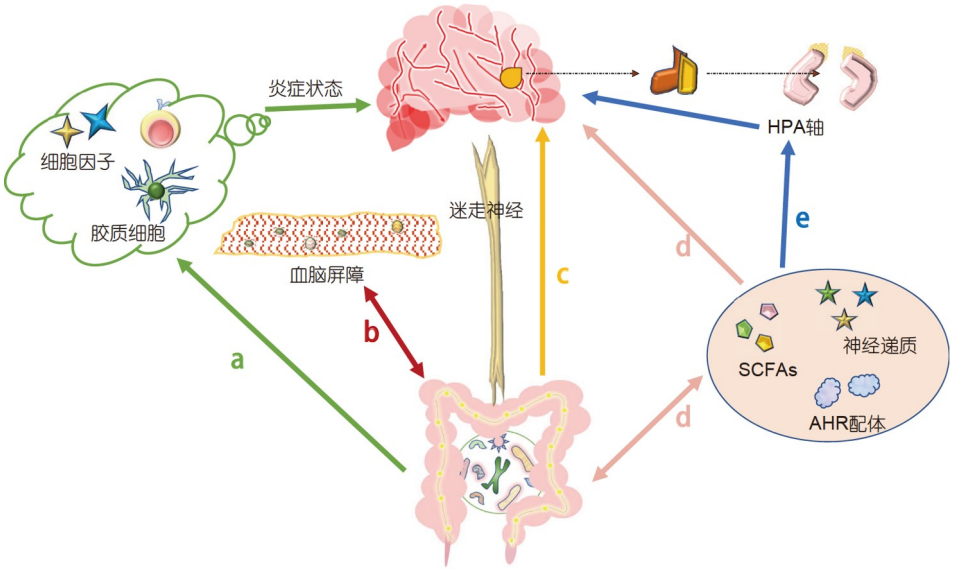

图 2 脑-肠轴及其与肠道菌群的关系. (a)肠道菌群调节脑部免疫反应和神经炎症状态; (b)肠道菌群调节血脑屏障; (c)肠道菌群通过迷走神经与中枢神经系统交流; (d)肠道菌群通过其代谢物参与脑部生理活动; (e)肠道菌群通过短链脂肪酸刺激下丘脑-垂体-肾上腺轴(HPA轴), 从而影响神经系统(网络版彩图)

Figure 2 The relationships between gut-brain axis and gut microbiota. (a) The gut microbiota modulates the immune response and neuroinflammatory state of the brain; (b) the gut microbiota modulates the blood-brain barrier; (c) the gut microbiota communicates with the central nervous system through the vagus nerve; (d) the gut microbiota participates in the physiological activities of the brain through its metabolites; (e) the gut microbiota influences the nervous system through stimulation of the hypothalamic-pituitary-adrenal axis (HPA axis) by short-chain fatty acids (color online)

治疗方法, 也有望用于呼吸道疾病的治疗[64].

2　肠道菌群与疾病

2.1　代谢性疾病

代谢性疾病是一类最为常见的疾病, 它是指人体中的脂肪、糖、蛋白质和嘌呤等一些物质代谢异常, 导致营养物质累积或缺乏所引起的疾病; 许多代谢性疾病与肠道菌群密切相关(表1). Chen等人[67]通过对338人4年前后51种表型和1183种血液代谢物的研究, 揭示了肠道微生物组成稳定性与宿主生理代谢之间的关联变化, 表明肠道菌群存在着个体特异性, 可开发用于预测宿主表型的微生物图谱(fingerprinting). 此外, 他们还报道了190种与宿主表型相关的微生物关联物及519种与血浆代谢物相关的微生物关联物, 发现肠道菌群可以通过其代谢物影响宿主的心血管健康.

肥胖症及其相关的发病率和死亡率在过去几十年急剧上升, 肠道菌群的改变是肥胖症的潜在原因之一[68,69]. 最常见的糖尿病[70~73]、心血管疾病[68]等许多代谢性疾病的发生也与肠道菌群密切相关(图3). 多个研究证实, 肥胖患者体内厚壁菌门与拟杆菌门比值上升, 这种变化与肥胖和胰岛素抵抗相关[74]. 在肥胖症患者和2型糖尿病患者的肠道中, 菌群的多样性也明显降低[75]. 无菌小鼠的体脂比野生型小鼠低, 表明在没有菌群定植的情况下, 小鼠的能量收集能力减弱[51]. Turnbaugh等人[76]发现, 将肥胖小鼠的粪便菌群移植到无菌小鼠中, 无菌小鼠的体重大幅增加; 反之, 若肥胖小鼠接受了来自瘦鼠的粪便菌群, 在不改变食物摄入的情况下, 肥胖小鼠的体重减轻. 这些都表明, 肠道菌群会影响宿主的能量吸收和储存, 且肠道菌群的紊乱与肥胖的发生密切相关[23,77].

高脂饮食是导致肥胖的关键因素之一, Druart等人[78]的报道表明, 高脂饮食喂养的小鼠处于轻微内毒素血症和轻微炎症状态, 会显著增加肥胖和糖尿病等代谢疾病的发生率. 而肠道菌群的改变会增加肠道黏膜的通透性, 增加脂多糖的渗入[79], 从而激活免疫信号通路, 导致慢性、轻型的炎症反应[23], 进一步说明了肠道菌群介导代谢性疾病发生的机制(图4). 肠道菌群代谢高脂饮食时产生的乙酸盐会触发副交感神经活动, 促进胃饥饿素、胰岛素的增加, 从而形成正反馈循环, 增加肥胖的可能性[80]. 与减肥相关的膳食化合物, 包括蔬菜、纤维和酸奶等, 都会改变肠道菌群的组成, 且这些影响部分是通过食物衍生的代谢物与免疫系统的相互作用介导的[81]. 二甲双胍是肥胖型2型糖尿病治疗的首选药, 可以影响肠道菌群[82]; 二甲双胍增加了小鼠体内Akk菌的丰度和能产生黏液的杯状细胞的数量[83]. 作为益生菌, Akk菌可增强宿主糖耐量, 通过诱导Tregs依赖性反应减轻脂肪组织炎症[84], 从而改善人体代谢状况.

其他的代谢性疾病同样和肠道菌群具有相关性, 如非酒精性脂肪肝的患病程度与菌群基因的丰度呈负相关, 与肠道内的变形菌门(Proteobacteria)、放线菌门丰度呈正相关, 与肠道菌群氨基酸的代谢也呈正相关[85,86]. 肠道菌群的代谢产物也会影响宿主代谢[87], 如短链脂肪酸[88]和胆汁酸有助于宿主心血管健康; 氧化三甲胺[89]则导致动脉粥样硬化和血栓的形成. 个性化饮食干预、益生菌/益生元或微生态制剂是预防和治疗心血管疾病[90,91]或其他代谢性疾病的备选方案[92].

2.2　免疫相关疾病

自身免疫性疾病是指免疫系统异常敏感、反应过

表 1　菌群和代谢性疾病的关系[a)]

Table 1　The relationship between the gut microbiota and the metabolic diseases[a)]

疾病种类	菌群变化	菌群相关代谢物	改善疾病相关菌群
肥胖症	厚壁菌/拟杆菌[60]↑	短链脂肪酸[17]、琥珀酸[72]	普氏菌[135]、艾克曼菌[139]
2型糖尿病	厚壁菌/梭状芽孢杆菌[57]↑ 拟杆菌/大肠杆菌[58]↓ 梭状芽孢杆菌[59]↑	丁酸盐[22]、琥珀酸[72]	艾克曼菌[71] 乳酸菌、双歧杆菌[137]
非酒精性脂肪肝	放线菌门[70]↑ 变形菌门、肠杆菌门[71]↑	胆汁酸[25]	鼠李糖乳酸杆菌[76]
心血管疾病	拟杆菌/厚壁菌门[75]↑	氧化三甲胺[27]、短链脂肪酸[73]	相关益生元[27]

a) 表中“↑”表示菌群相对丰度增加, “↓”表示菌群相对丰度减小

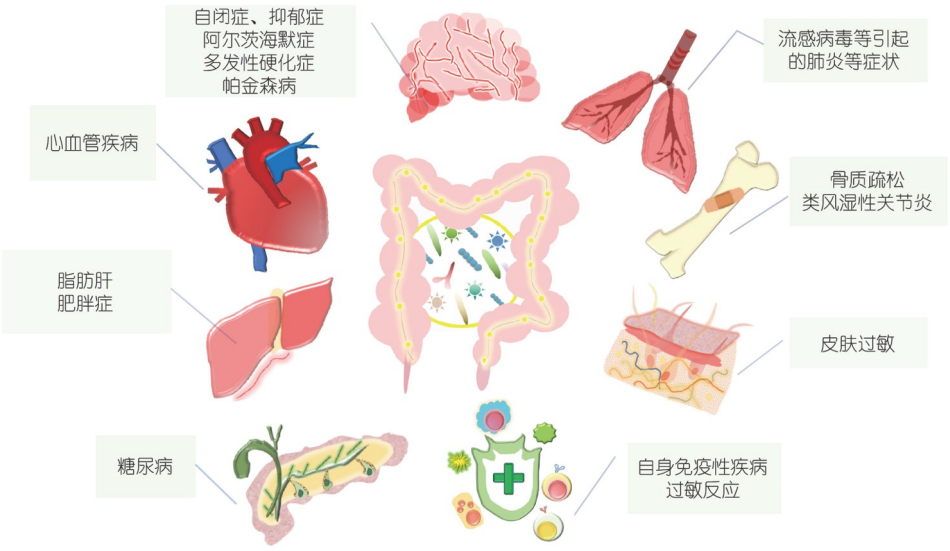

图 3 与肠道菌群相关的多种疾病(网络版彩图)
Figure 3 Diseases related with the gut microbiota (color online)

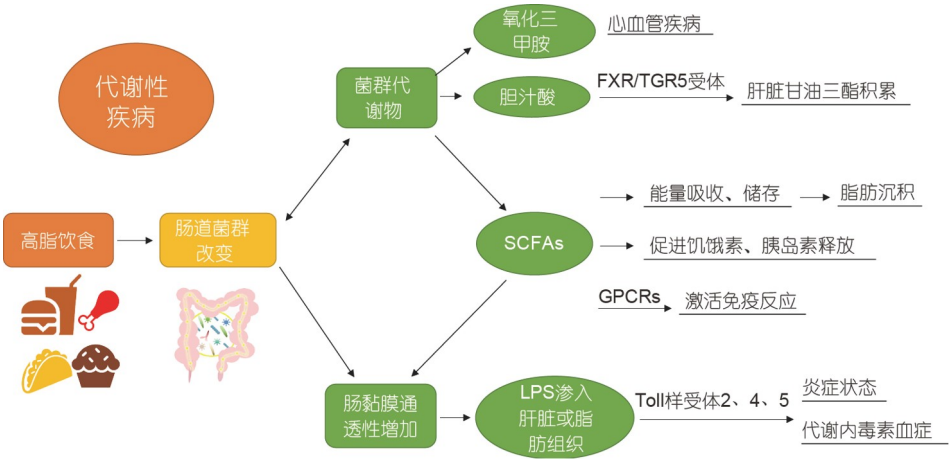

图 4 肠道菌群介导代谢性疾病发生的机制(网络版彩图)
Figure 4 The mechanism of gut microbiota mediating the occurrence of metabolic diseases (color online)

度, 将自身物质当作外来异物进行攻击而引起的疾病. 肠道菌群与多种自身免疫性疾病有关, 包括炎症性肠病、类风湿关节炎、多发性硬化症(multiple sclerosis, MS)、银屑病等. 克罗恩病和溃疡性结肠炎是两种最具代表性的慢性肠道炎症性疾病, 称为炎症性肠病(inflammatory bowel disease, IBD). IBD患者存在肠道屏障的改变, 这种改变会导致菌群和微生物代谢产物的失调[93], 从而诱导免疫细胞激活及肠道炎症[94], 导致宿主产生病理反应. IBD患者的肠道菌群中, 普氏菌和产丁酸盐的柔嫩梭菌(*Clostridium tenuis*)等有益菌的丰度下降, 可能是导致疾病症状产生的原因[95~97]. 通过靶向调控特定菌群(如增加产短链脂肪酸的细菌丰度)或粪菌群移植调控人体的肠道菌群, 已成为临床治疗IBD患者的一种有效方案[98,99].

类风湿性关节炎是一种全身性、炎症性的慢性疾病, 该疾病也和肠道菌群之间存在联系[100]. 相比对照组, 早期类风湿性关节炎患者的微生物组成发生明显改变, 具体表现为双歧杆菌(*Bifidobacterium*)和拟杆菌数量的减少[101]及普氏菌属数量的增加[102]. 给予药物针对性治疗后, 失调的肠道菌群会部分恢复正常[103].

目前，特定的微生物类群可能成为类风湿性关节炎靶向治疗的可行药物靶标[100].

过敏反应包括食物过敏、特应性皮炎和哮喘等, 是异质性炎症免疫介导的疾病. 过敏症的流行演变与环境和生活方式的剧烈变化密切相关. 工业化和城市化发展、过度医疗和抗生素滥用、运动的缺乏和高度加工的饮食等变化会引起生命早期微生物暴露减少、多样性丧失[104], 从而导致机体对部分环境过敏原的超敏反应. 肠道菌群可以通过影响IgE-嗜碱性粒细胞轴、Th1/Th2细胞的平衡、Toll样受体信号通路、Tregs的激活等机制, 来影响过敏反应[9]. 对特应性过敏症高危婴儿的研究发现，婴儿早期变形菌门的减少和Toll样受体TLR-4的增多相关; 而瘤胃球菌属的减少和TLR-2的增多相关，这些变化都会诱发婴儿的先天炎症反应[105]. 婴儿肠道菌群中的大肠杆菌(*Escherichia coli*)和艰难梭菌(*Clostridioides difficile*)的丰度增高[106,107]、双歧杆菌的丰度降低[108]，这些肠道菌群的变化与儿童过敏性疾病风险的显著增加相关.

2.3　神经系统及精神类疾病

肠道菌群和中枢神经系统之间存在双向交流通路, 而该通路的失调涉及到了许多神经系统疾病. 越来越多的临床和临床前研究表明，肠道菌群可能是阿尔茨海默病、帕金森病、抑郁症、自闭症谱系障碍(autism spectrum disorders, ASD)、多发性硬化症等神经系统疾病的关键易感性因素.

MS是一种中枢神经系统自身细胞免疫性疾病, 其发病因素和治疗方法均和肠道菌群密切相关, 如MS患者肠道菌群中柔嫩梭菌、普氏菌[109]、拟杆菌[110]的丰度显著降低; 口服乳酸菌[111]、补充脆弱拟杆菌[112]等能够修正肠道菌群失调, 缓解MS症状. 帕金森病在临床上主要表现为运动障碍, 研究发现, 帕金森病患者肠道菌群中肠杆菌属增加、普氏菌属减少[113]. 肠杆菌的增加会使得具有调节黑质纹状体神经元功能的促胃液素减少[114]; 普氏菌的减少可能会抑制短链脂肪酸等抗炎物质的产生, 从而损伤肠道黏膜屏障[115].

抑郁症是最普遍的精神性疾病之一，严重影响患者的生活质量. 免疫系统失调、压力过大和肠道菌群失衡会引发抑郁症[116]. 越来越多的研究证明，抑郁症的发生与菌群密切相关[67]，且肠道菌群中部分微生物的丰度和抑郁症的严重程度相关[117]; 与健康人相比，抑郁症患者粪菌中拟杆菌门、变形菌门和放线菌门的丰度显著升高, 而厚壁菌门的丰度显著降低; 抑郁症患者体内肠杆菌科(Enterobacteriaceae)和另枝菌属(*Alistipes*)的丰度升高; 粪杆菌属(*Faecalibacterium*)的丰度与抑郁症的严重程度呈负相关，与健康人相比，粪杆菌属微生物在抑郁症患者体内的丰度较低. 抗生素治疗会扰乱肠道菌群，增加抑郁和焦虑的风险. 一些肠道菌的代谢物也会影响人体等宿主的精神状态，如来自细菌的代谢物4-乙基苯基硫酸盐是一种与神经发育障碍相关的尿毒症毒素，可诱导小鼠产生类似焦虑的行为[118]. 传统的抗抑郁药物起效慢、副作用大，部分情况下会降低患者的依从性. Miyaoka等人[119]在对耐药抑郁症患者使用抗抑郁药物的同时，对他们进行了8周的益生菌辅助治疗，这些治疗显著改善了抑郁症症状[119]. 肠道菌群与ASD相关，ASD患儿的肠道菌群与健康儿童不同; 缺失特定细菌的动物表现出自闭症样症状; 将ASD患者的肠道菌群移植给无菌小鼠可引起行为变化，而饮食干预或摄入益生菌可改善ASD患儿的行为症状[120].

2.4　癌症

癌症是严重危害人类健康的主要疾病，2020年全球死于癌症的人员接近千万. 多项研究表明，肠道菌群与多种肿瘤的发生相关，参与肿瘤转化、肿瘤进展以及抗肿瘤治疗的免疫反应等过程. 癌症的发生可能是由于肠道菌群从降解纤维菌群向代谢碳水化合物和氨基酸菌群转变的过程，且与菌群脂多糖代谢的增加有相关性[121].

结肠、直肠癌是由肠道菌群的逐步紊乱引起的, 由不当饮食、致癌基因和抑癌基因等改变共同引发[122,123]. 一些特定的微生物通过激活炎症反应、破坏有保护作用的肠黏液层, 创造有利于肿瘤生长的环境, 如幽门螺旋杆菌破坏胃部正常酸性环境[124]. 产肠毒素脆弱拟杆菌(enterotoxigenic *Bacteroides fragilis*, ETBF)可以通过分泌特定的肠毒素，来诱发溃疡性结肠炎和结肠、直肠癌[125]. 研究表明，梭杆菌(*Fusobacterium*)在肿瘤发展过程中起着主导作用，腺瘤及邻近正常黏膜活检显示肿瘤组织中梭杆菌阳性率高于正常组织; 梭杆菌可以通过招募肿瘤浸润免疫细胞，产生促炎微环境，从而促进结直肠肿瘤进展[126]. 实验表明，肠道菌群有能力穿越黏膜或血液屏障，并在乳腺组织、精

囊等实体器官中建立独特的菌群，这可能解释了微生态失调和结肠癌、胃癌、食道癌、胰腺癌、喉癌、乳腺癌和胆囊癌风险增加之间的关联[122].

共生的肠道细菌也可以帮助宿主对抗肿瘤，它们能够减少次级胆汁酸分泌，同时增加具有广泛抗肿瘤作用的发酵产物(如丁酸盐). 这些机制可以对抗致癌信号通路，如抑制组蛋白去乙酰化酶的活性，能够促进肿瘤细胞凋亡，抑制肿瘤增殖和阻止肿瘤转化等[127~129]. 研究发现, 肠道菌群提高了基于PD-1抑制剂免疫治疗抑制上皮肿瘤的疗效，表明改善肠道菌群有助于对抗癌症[130].

2.5 其他疾病

流感病毒感染可以改变肠道菌群的组成，导致免疫失调，促进炎症性肠道疾病的发展[131]；一些肺部流感病毒感染者也会出现胃肠道紊乱的症状[132]. SARS-CoV-2病毒能够在人类肠上皮细胞中复制，在粪便样本中也可以检测到SARS-CoV-2病毒；COVID-19患者的肠道菌群也发生了变化，其菌群的组成与疾病的严重程度相关；相比健康人群，COVID-19患者体内具有免疫调节潜能的细菌数量大量减少，如柔嫩梭菌群、粪杆菌、直肠真杆菌(*Eubacterium rectale*)和双歧杆菌的数量在COVID-19患者体内减少[133]. 肠道菌群可以通过激活免疫系统来抵抗病毒感染，如通过Ⅰ型干扰素(interferon，IFN)信号通路调节人体免疫稳态[62]. 此外, 微生物群衍生的代谢物也具有抗病毒作用, 如乙酸盐可通过GPR43激活，调节肺上皮细胞中的免疫应答, 从而抑制呼吸道合胞病毒(respiratory syncytial virus, RSV)的感染[22].

肠道菌群是骨骼成熟和骨骼健康的重要调节因子，由雌激素缺乏、糖皮质激素和糖尿病而引起的骨病和肠道菌群密切相关[134]. 研究发现，与常规饲养的小鼠相比，无菌饲养小鼠的骨密度、骨体积和骨骼结构发生了改变[135,136]. 除了动物实验, 人体实验也证实了菌群与骨骼发育具有相关性. 研究发现，骨质稀少或骨质疏松的受试者肠道菌群中，六个菌属的丰度与健康对照组有显著差异，表明骨密度的降低与肠道菌群的改变有关[137]. 与骨质形成相关的肠道菌群可以在小鼠个体之间传播，表明通过粪便微生物组可能改变骨骼表型[134]，为改善骨质健康提供了新的治疗思路.

3 改善肠道微生态的措施

3.1 菌群检测和精准医疗

精准医疗, 也称个性化医疗, 是根据个体的基因、微生物群、环境、生活方式等进行个性化医疗诊断和治疗的医学方案. 个体与个体之间的肠道菌群的组成存在很大的差异，短链脂肪酸和胆碱等菌群代谢物的含量也具有个体差异性[138], 这将导致不同个体在同种疾病的诊断和治疗上存在很大差别[139], 从而大大降低疾病诊治的效果. 肠道菌群与药物的直接或间接相互作用，影响了药物的药理和毒性作用；肠道菌群可以通过直接的代谢作用使药物失活、激活、改变药效或增加药物的生物利用度，这些相互作用可能导致药物失效致患者死亡[139,140]. 因此，关注肠道菌群对个性化精准医疗意义重大.

随着高通量测序和培养组技术的出现，科学家已在人体微生物群的计数、表征和分类方面取得了多项进展. 肠道菌群检测方法的发展加强了基于微生物群落的疾病预防、诊断和治疗，更有助于基于营养、微生物和药物干预的个性化治疗方案的发展(图5). 早期检测微生物组组成的主要方法是16S rRNA基因测序法，该方法存在较多的局限性，难以对微生物进行菌株水平的鉴定和分类[141]. 为了更加准确地了解人体微生态系统，宏基因组学、宏蛋白质组学和宏代谢物组学等多组学的整合应用可以更准确、直接地解读肠道菌群的功能特性[142,143](图5). 多组学可以同时测量宿主和微生物表达蛋白的水平以及肠道中存在的膳食成分；这些结果可以反映宿主和肠道菌群相互作用的状态，能够用于区分不同的炎症状态，作为肠道稳态的指纹图谱[144]. 多组学方法应用于临床诊断，将阐明肠道菌群的组成及微生物群-宿主的相互作用关系，为实施个体化精准治疗提供指导方案[145]. 通过多种可视化方法和培养组学, 能够验证肿瘤中细菌的种类, 并标记它们在癌症和免疫细胞中的定位，为肿瘤的早期诊断开拓新途径.

3.2 饮食调控

研究证实，宿主遗传对于宿主菌群组成的影响是有限的[146]，外部因素，如饮食干预可以影响宿主的菌群组成, 高脂饮食与拟杆菌丰度增加有关; 高纤维摄入与普氏菌丰度增加有关[147,148]. 饮食结构还会影响短链

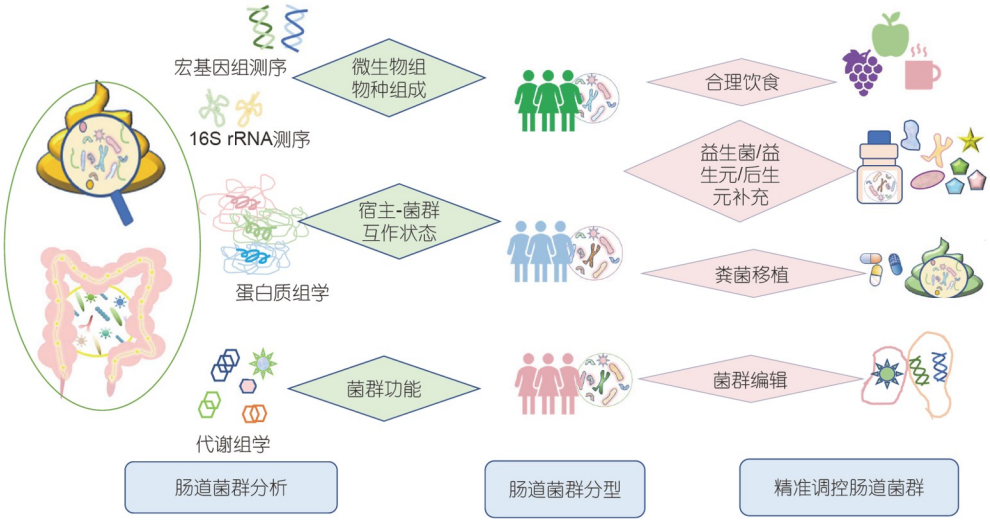

图 5　肠道菌群检测和调控的方法/策略(网络版彩图)
Figure 5　The methods and strategies used for gut microbiota diagnosis and modulation (color online)

脂肪酸、脂多糖、胆汁酸和支链氨基酸等肠道菌群代谢产物的产生[13]. 地中海饮食是一种以蔬菜水果、鱼类、五谷杂粮、豆类和橄榄油为主的饮食, 这种饮食结构可以为人体提供必要的营养物质, 促进人体健康[149], 降低患慢性疾病的风险. 相反, 不均衡的饮食结构会导致肠道菌群紊乱, 诱发促炎细菌的增殖, 甚至会增加罹患癌症的风险, 如西式饮食(富含加工食品、糖和脂肪)的流行与肥胖、糖尿病[150]和心血管疾病的发病率增长有关[151]. 根据个体肠道菌群, 积极调整饮食结构, 对促进健康和缓解多种疾病具有积极作用(图5).

益生菌可以改善宿主微生态平衡, 拮抗肠道病原体, 保护宿主肠道免受外源性病原体感染. 常用的益生菌主要包括乳酸菌、双歧杆菌、酪酸梭菌、嗜酸乳杆菌、酵母菌、Akk菌[152]等. 研究发现, 受试者连续服用2个月的多元益生菌(含乳酸菌种、双歧杆菌种和链球菌种), 可以逆转肠道菌群紊乱, 具有抗炎作用[53]. 除了口服发挥保健作用的一代益生菌, 二代益生菌利用特异性菌株作为载体, 将治疗疾病的分子靶向递送至相关组织和器官, 定向发挥疾病诊疗的作用[153]. 益生元是一种人体等宿主不可消化的膳食化合物; 它通过选择性地调节某些肠道细菌的数量或活性, 促进人体等宿主的健康[154]. 低聚果糖、乳果糖、菊粉和木聚糖寡糖等食物中的益生元能够显著改变肠道菌群[12]. 膳食纤维和短链脂肪酸对过敏性疾病、炎症性疾病以及呼吸道感染具有预防作用[22].

中药益生菌发酵产物在促进人体等宿主健康, 提高宿主免疫方面发挥重要的作用. 通过系统生物学解析中药、益生菌等与肠道菌群、宿主健康之间的因果关系, 并应用合成生物学技术大量合成中草药植物中的微量活性天然产物[155~158], 将有助于多种益生元、合生元等促进宿主肠道菌群健康产品的研发, 从而为人体等宿主的健康做出贡献.

3.3　菌群移植

粪菌移植, 是指将健康人群肠道中的功能菌群移植至患者胃肠道内, 重建具有正常功能的肠道菌群, 以此达到治疗疾病的目的; 粪菌移植也是一种特殊的“器官移植”. 临床研究表明, 利用粪菌移植治疗艰难梭状芽胞杆菌感染、溃疡性结肠炎等疾病具有良好的前景[159,160]. 肠道疾病患者合并存在的肺炎、哮喘、肝病、糖尿病、皮肤病、造血功能异常、癫痫、自闭症、睡眠障碍等并发症, 大多能通过粪菌移植重建患者肠道菌群得到缓解甚至治愈[161]. 粪菌移植的技术正在逐步走向成熟, 目前已经发展出冷冻粪便[162]、粪菌胶囊[163]等粪菌制备技术. 由于缺乏专门的粪菌保存中心、难以招募合格粪菌捐助者和粪菌安全性等问题, 该技术还未大规模推广应用[164]. 为了克服粪菌移植中的这些障碍, 科研人员在供体筛选、粪便样本制备、样本库、临床管理和粪菌移植中心的实施等方面进行

了完善，粪菌移植有望在临床治疗疾病中得到普遍应用[165,166]. 此外，自体粪菌移植技术也得到不断发展. 研究表明，在抗生素扰乱小鼠肠道菌群后，自体移植抗生素处理之前的肠道菌群可以帮助小鼠快速恢复至使用抗生素前的正常菌群平衡状态[167]. 虽然粪菌移植已得到一些推广和应用，但仍存在一定的安全性风险. 在未来，如何筛选获得安全性高、疗效显著的粪菌将成为粪菌移植推广应用的主要挑战之一.

3.4 微生物组靶向调控技术

合成生物学工具使人们能够合理地设计和定向改造微生物，调控微生物-宿主和微生物-微生物的相互作用，从而达到生物治疗疾病的目的[168]. 定向改造后的工程菌在预防病原感染、调节宿主免疫和代谢等方面都被证实有良好效果. Drolia等人[169]利用创建的酪乳杆菌工程菌株针对性地预防李斯特菌感染，这种策略可以强化益生菌的作用，提高益生菌靶向预防特定病原菌感染的效率. 通过精准编辑的肠道菌群，靶向促肿瘤肠杆菌的代谢，可以降低肠炎小鼠肠癌的发生率[170]. 在慢性肠道炎症中，微生物组靶向调控代谢技术有望抑制肠道菌群失衡引发的恶性肿瘤. 研究人员将肠道细菌进行基因编辑，让细菌产生能够调节人体新陈代谢、治疗相关疾病的分子，并将基因编辑过的肠道菌群植入小鼠体内后，这些小鼠出现了血糖水平降低等显著的代谢变化[171].

相比于单种细菌的编辑，合成微生物群落是人工合成的多个物种共培养的微生物体系(包括野生型和基因组改造的微生物)，即对微生物群落进行精准调控和改造的人工微生物体系[172]，该方法在精准医疗等领域具有很好的应用潜能[173]. 相比于传统的菌群移植手段，微生物组的靶向调控技术具有细菌组成明确、基因易操控、与宿主的相互作用清晰、可重复制备等优势，未来在肠道菌相关疾病的防治、促进人类健康等方面将发挥重要作用[173]. 肠道菌群与口腔、胃等菌群的微生物组密切相关. 在研究肠道菌群的同时，也需加强对宿主基因组、转录组等多组学及口腔、胃等肠道菌群的整合研究，从整体上解析肠道菌群与宿主之间的关系[124].

4 总结与展望

肠道菌群对人体等宿主健康状态影响较大. 肠道菌群能够与免疫系统互作，通过各种代谢产物，脑-肠轴、肺-肠轴等影响人体生理代谢和健康状态. 维持肠道菌群的稳态是保持人体等宿主健康的必要条件. 多种疾病的发生发展与肠道菌群密切有关，一旦肠道菌群的稳态被打破，宿主的健康也会受到影响，甚至发展出各种疾病. 肠道菌群与宿主的相互作用非常复杂，目前仍需要更为细致全面的基础研究，才能更好地阐明肠道菌群与多种疾病之间的作用机制及因果关系. 同时，肠道菌群具有个体特异性，这种差异性会使不同个体对于同种药物的代谢产生差别. 因此，解析个体肠道菌群的状态是实施个性化精准诊疗的重要环节之一. 发展基于微生物组学的个性化菌群检测方法，在肠道菌群与人体健康的因果关系研究方面取得突破，建立具有当地特色的人体肠道菌群数据库和实体库等，将有利于个体化菌群在疾病诊疗方面取得更大进展.

饮食与肠道菌群的组成和功能密切相关，饮食结构会影响宿主菌群组成和菌群代谢. 饮食中添加的益生菌、益生元和合生元等对于维持肠道健康有很大作用. 粪菌移植、菌群靶向调控合成等改善肠道微生态的技术日趋成熟，在临床应用上具有很好的应用前景. 目前，饮食结构调整、益生菌/益生元补充、粪菌移植等方法在临床上对于部分患者的疾病治疗已取得了一些成效，但精准调控菌群的技术尚处于起步阶段，相关的研究也不够全面，临床应用前仍需要更多的基础研究数据支撑. 未来，基于个性化肠道菌群检测，结合肠道菌群与疾病因果关系，将为多种疾病患者提供精准营养和个性化诊疗方案. 从菌群角度着手，有望为提高人体健康水平提供新思路和新方向，为治愈多种复杂疾病提供理论基础.

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Recent advances on the recovery, modulation and synthetic biology of gut microbiota and hosts

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Gut microbiota is closely related to host health. The interactions between gut microbiota and hosts are complex, including the relationships between microbiota and the immune system, gut-brain axis, gut-lung axis etc. Gut microbiota disorders are related to the occurrence and development of some diseases, and some microbial strains are identified to be the cause of some diseases. Moreover, gut microbiota has effects on drug metabolism, and the individual differences of gut microbiota might lead to the different individual effects of the same drug. Therefore, recovering individual gut microbiota is essential for the implementation of individual precision medical treatment. Gut microbiota is alterable, and gut microbiota can be modulated at healthy state by dietary regulation, probiotics/prebiotics/synbiotics supplement, and fecal microbiota transplantation. Besides, microbiota editing techniques and synthetic microbiota have been applied in the modulation of gut microbiota. Currently, modulation of gut microbiota has become one of the effective strategies to improve or cure some diseases. This review summarized the interactions between gut microbiota and hosts, the correlations and causal relationships between gut microbiota and diseases, the ways to improve human health by modulating gut microbiota, and gave insights into the application of microbiome and synthetic biology on the modulation and synthesis of gut microbiota.

gut microbiota, host-microbe interactions, short-chain fatty acids, microbiota modulation, microbiome, synthetic biology

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