

肠道微生物间互作及其代谢物发挥作用的研究进展

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摘要 肠道是一个完整的生态系统, 不同微生物间通过中立、共生、竞争和捕食等方式形成了复杂的微生态关系网络, 进而影响宿主的健康. 正常情况下, 肠道微生物间处于动态平衡的状态, 当受到内部和/或外界因素影响后, 肠道微生态也会发生相应的变化. 值得注意的是, 该变化不仅是单个微生物丰度的改变, 更多的是该微生物互作关系网络内微生物群的变化, 进而导致肠道微生物整体多样性、结构、功能和代谢物水平的改变. 此外, 菌群代谢物是肠道微生物与宿主互作的主要媒介, 短链脂肪酸和胆汁酸等关键的菌群代谢物可与宿主直接对话, 并在机体营养吸收、代谢、免疫系统发育和病原体防御等方面发挥着重要作用. 因此, 本文总结了肠道微生物间的互作关系, 并讨论了肠道微生物通过产生关键代谢物与宿主互作的方式, 为深入了解微生物间互作及其代谢物对宿主健康的潜在作用提供参考.

关键词 肠道微生物, 代谢物, 互作关系, 宿主健康

肠道菌群被认为是人体重要的“器官”, 参与机体的营养吸收、激素代谢和免疫调节等生理过程. 近年来, 随着高通量测序技术和组学技术的发展, 研究人员对肠道微生物群落的复杂性及其内部的调控机制有了更深入的了解^[1,2]. 肠道微生物群落包括细菌、真菌、古细菌、病毒、寄生虫等微生物, 这些微生物相互作用, 形成了一个数量庞大、结构复杂、功能强大的生态系统. 在正常的生理状况下, 肠道中微生物是一个动态平衡的状态, 肠道微生物间也并非独自发挥作用的, 而是具有复杂的相互作用网络关系^[3,4].

目前, 宿主与微生物间的关系主要是互生关系, 宿主可以为肠道提供良好的生态环境, 使肠道细菌可以生长, 肠道中微生物则可以通过多种代谢反应贡献于宿主的健康. 肠道微生物间的关系主要有: 共生、竞争、捕食和中立等^[5]. 共生关系中, 一些微生物相互提

供彼此需要的营养物质或生存条件, 而在竞争关系中, 微生物之间争夺有限的资源, 如营养和生存空间. 正常情况下, 各种微生物相互竞争, 又相互依存, 共同维系着肠道菌群的稳态, 并在宿主的生长发育、代谢吸收、免疫调节等方面发挥重要作用. 明确肠道微生物间的互作模式对于解析其与健康间的潜在关系中具有重要意义, 因此本文总结了肠道中细菌间互作关系方式, 并讨论了肠道微生物通过产生关键代谢物与宿主互作的具体方式, 以期肠道菌群与健康间的关系提供新的见解.

1 肠道微生物间的互作关系

1.1 肠道细菌间的互作关系

细菌是微生物群落生态学中研究最多的微生物之

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一, 细菌间的互作关系十分复杂, 涉及多种生物学过程(图1). Jiang等人^[5]选取了24个细菌菌株与人类肠道微生物生物库中的19个细菌菌株进行成对培养, 发现细菌群落间的相互作用大多为中立(51.67%), 其次是偏利共生(21.67%)、偏害共生(18.33%)、竞争(5%)和捕食(3.33%).

中性或有益的相互作用可以被定义为共生, 互利共生是微生物之间相互作用的一种特殊机制, 即一些微生物能够相互提供对方所需的营养物质或生存条件从而共同获益. McCully等人^[6]将大肠杆菌(*Escherichia coli*)与沼泽红假单胞菌(*Rhodopseudomonas palustris*)共培养, 研究发现大肠杆菌发酵葡萄糖排出的有机酸为沼泽红假单胞菌提供碳源, 沼泽红假单胞菌将 N_2 转化为 NH_4^+ , 为大肠杆菌提供必需的氮源. Soto-Martin等人^[7]研究了产丁酸盐的人肠道细菌菌株对两种生长因子(维生素和氨基酸)的需求, 对具有不同原营养细菌(能够产生生长因子的细菌)的硫胺素或叶酸营养不良菌株(不能产生生长因子的细菌, 需从外部来源获得)进行了合成共培养试验, 结果表明细菌之间确实发生了交叉喂养, 彼此受益于其他群落成员提供的生长因子. 偏利共生指一种细菌从另一种细菌中受益, 而后者既不受益也不受害. 例如, 一些细菌利用其他细菌产生的

代谢废物作为营养源. 多形拟杆菌(*Bacteroides thetaio-taomicron*)是一种能够分解复杂多糖的肠道细菌, 其代谢活动生成短链脂肪酸、氢气和二氧化碳等代谢产物. 史密斯甲烷杆菌(*Methanobrevibacter smithii*)是一种产甲烷的古细菌, 它能够利用多形拟杆菌的代谢产物, 如氢气和二氧化碳, 通过甲烷生成途径获取能量^[8].

竞争、偏害共生和捕食属于对抗性相互作用, 在自然条件下, 生活在肠道中的细菌在种间种内对空间和营养的竞争非常激烈^[9,10]. 竞争是指两个或多个微生物为了生存和繁殖所需的同一有限资源进行争夺, 细菌间通过积累和储存所需要的营养物质, 抑制其他竞争菌的生长. 例如细菌间对铁的竞争, 铁是参与氧运输、电子转移、生长、DNA合成的必需微量元素, 是许多酶的辅因子^[11]. 通常, 铁通过铁载体被细菌吸收^[12], 细菌间通过分泌铁载体来竞争铁离子^[13,14]. 典型的细菌铁载体是由肠杆菌科的大肠杆菌、沙门氏菌(*Salmonella*)和肺炎克雷伯氏菌(*Klebsiella pneumoniae*)分泌的肠杆菌素(entobactin, Ent), 它参与宿主转铁蛋白中铁的回收, 使得病原菌在生存环境中占据竞争优势. 细菌间还通过占据结合位点的方式相互竞争, 包括细菌对宿主细胞表面受体或生物膜的特定附着点的占据^[15]. 具有良好黏附能力的益生菌附着在肠黏膜上, 可

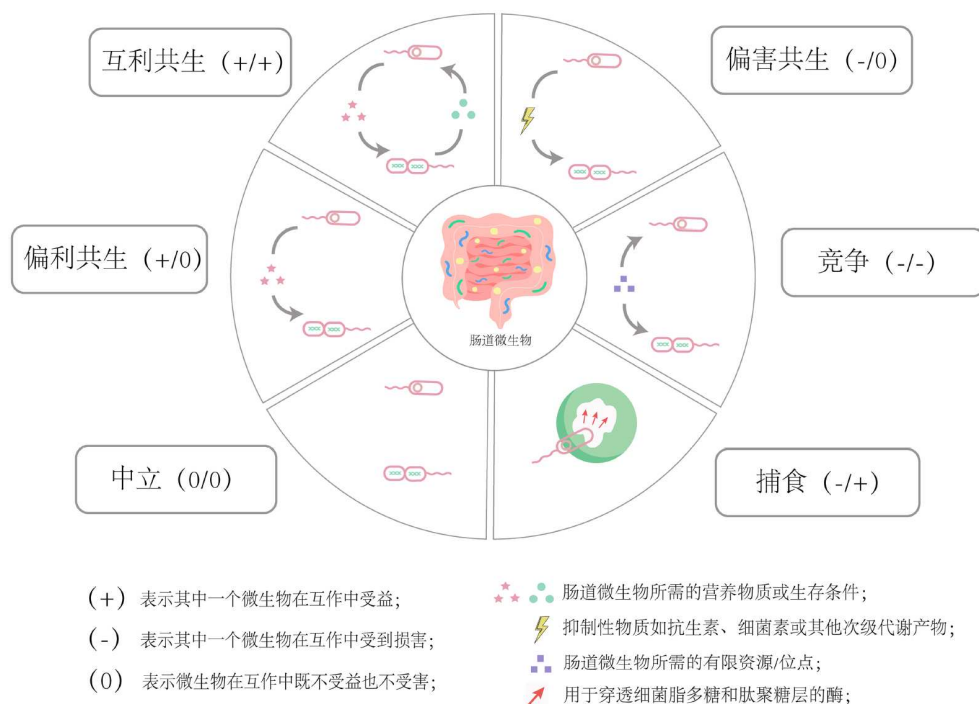


图1 (网络版彩色)肠道中微生物群落的互作类型

Figure 1 (Color online) Types of interactions of gut microbiome

以通过竞争宿主细胞结合位点来对抗肠道病原体。植物乳杆菌0612(*Lactiplantibacillus plantarum* 0612)被证实可以有效地竞争肠上皮细胞的受体位点,阻止大肠杆菌和单核细胞增生李斯特菌(*Listeria monocytogenes*)的定植^[16]。此外,微生物互作中的偏害共生是指一种微生物通过产生抑制性物质如抗生素、细菌素或其他次级代谢产物来实现对另一种微生物产生抑制或损害作用。由细菌分泌的具有杀菌和抑菌功能的分子在驱动细菌菌株之间的相互竞争中发挥关键作用, Kienesberger等人^[17]发现肠道克雷伯氏菌产生肠毒素替利霉素,一种促突变的抗生素,进而抑制其他病原菌生长,为自己争取生存空间与资源。同样的,许多病原菌也通过携带细菌毒素用于与其他细菌的竞争^[18,19]。例如脆弱拟杆菌产生的抗菌蛋白,称为(膜攻击复合物/穿孔素)结构域蛋白,这种细菌素在抑制肠道内竞争细菌的生长方面起着重要作用,从而帮助脆弱拟杆菌维持其在肠道微生物群落中的生态位。除细菌代谢物外,产生抗菌毒素干扰竞争对手信号也是一种常见策略。据报道,芽孢杆菌(*Bacillus*)能够通过产生风霉素阻断金黄色葡萄球菌(*Staphylococcus aureus*)的信号传导途径,进而抑制其生长和活性^[20]。

肠道中还有一类细菌能够捕食并消耗其他细菌,如*Bdellovibrio bacteriovorus*和*Micavibrio aeruginosavorus*等表现出专门以捕食其他细菌为生的行为^[21],主动地以其他细菌为食。这些细菌通过识别并黏附在猎物上,通过释放酶穿过细菌脂多糖和肽聚糖层进入宿主的周质空间,获得生存和繁殖所需的营养,最终猎物细胞破裂死亡^[22]。有研究发现*Bdellovibrio bacteriovorus*和*Micavibrio aeruginosavorus*可减少肠道内中多重耐药细菌的丰度^[23]。

1.2 肠道细菌与真菌间的互作关系

真菌在人类肠道微生物中所占比例为0.1%^[24],是肠道微生物组中一个虽小但重要的组成部分。念珠菌属(*Candida*)和酵母菌属(*Saccharomyces*)在人类肠道真菌群落中占据主导地位,其多样性和丰度可能影响其他肠道微生物的组成以及它们之间的相互作用,协作和拮抗关系普遍存在于肠道细菌与真菌之间。

当前的微生物学研究领域中关于真菌与细菌间共生作用的研究较少。在一项体外研究中观察到热带念珠菌(*Candida tropicalis*)、大肠杆菌(*Escherichia coli*)和黏质沙雷氏菌(*Serratia marcescens*)协同作用生成强

大的生物膜^[25],其可能机制是增强致病潜力以及保护它们免受免疫细胞的攻击。Eckstein等人^[26]研究发现白色念珠菌(*Candida albicans*)与多形拟杆菌(*Bacteroides thetaiotaomicron*)共同存在于肠道中时,白色念珠菌会定位在由拟杆菌促进形成的外黏液层内部以促进其生长。此外,Zeise等人^[27]发现白色念珠菌促进哺乳动物胃肠道中的粪肠球菌(*Enterococcus faecalis*)生长。有趣的是,相比于单独感染其中一种病原菌,白色念珠菌与粪肠球菌的共同感染可以减少组织损伤并延长蠕虫的寿命,这表明真菌与细菌间的相互作用抑制了毒力^[28]。尽管这些相互作用在微生物生态和宿主健康中可能扮演着关键角色,但目前对于它们之间的互惠机制、协同效应等方面的理解仍然有限。

此外,肠道细菌通过一系列机制限制真菌的定植,例如产生抗真菌毒素和代谢物以及激活免疫途径来阻止真菌定植^[29-31]。乳杆菌属作为一类广泛分布于肠道中的微生物,常被认为是有益菌,其代谢产物在抑制白色念珠菌的生长及其向菌丝形态的转变方面表现出显著效果^[32,33]。例如由厌氧细菌发酵产生的短链脂肪酸(short chain fatty acids, SCFAs)是肠道微生物群落产生的代谢物之一,众多研究证实它们具有抗真菌特性,在维持宿主健康方面发挥关键作用^[34]。肠道细菌产生的SCFAs能够抑制白色念珠菌的生长,并且小鼠肠道中的SCFAs水平的降低与白色念珠菌的富集有关。真菌与细菌具有相似的表面生态位点,占据或竞争相似的生存空间和资源。除了直接分泌物质来抑制真菌,其相互作用还可能通过宿主免疫途径进行。在一项动物研究中发现,万古霉素治疗的小鼠肠道菌群多样性显著降低,宿主对白色念珠菌的易感性增强^[35]。值得注意的是,这种易感性的增加可能是由于分段丝状细菌(segmented filamentous bacteria, SFB)的减少^[35]。这种细菌的缺失会影响肠道淋巴组织辅助性T细胞17(T helper cell 17, Th17)细胞的分化和功能,进而减弱了依赖于粒细胞-巨噬细胞集落刺激因子(granulocyte-macrophage colony-stimulating factor, GM-CSF)和白细胞介素(interleukin, IL)17A的抗真菌免疫反应^[36-38]。

1.3 肠道细菌与噬菌体的互作关系

病毒作为肠道微生态系统的一个重要组成部分,对宿主的内稳态和机体健康发挥着至关重要的作用。噬菌体是肠道病毒组中的主要成员^[39],目前已知的肠道噬菌体组主要由DNA噬菌体组成,其中大多数属于

有尾噬菌体目(Caudovirales)和微小噬菌体科(Microviridae), 少部分属于长尾噬菌体科(Siphoviridae)^[40-42]。肠道细菌与噬菌体间的相互作用对维持肠道菌群结构和功能具有影响, 二者间的关系可以通过“杀死赢家”动力学(捕食者-猎物关系)和“红皇后假说”(寄生关系)来进行描述。噬菌体感染宿主细菌时具有专一性, 在健康成年人肠道内, 细菌与噬菌体通常维持一种稳定的动态平衡。被感染的细菌不断进化以躲避噬菌体的攻击, 同时噬菌体也不断发展新的感染策略, 这种相互适应实现了长期的平衡^[43]。

肠道中的噬菌体可以分为烈性噬菌体和温和噬菌体。“杀死赢家”动力学假说主要用来描述指烈性噬菌体与宿主间的关系。烈性噬菌体感染其宿主菌后, 裂解细菌并释放子代噬菌体。烈性噬菌体作为细菌的捕食者, 能够直接影响动物肠道内多种细菌的丰度、多样性以及代谢^[41,44]。Cornuault等人^[45]对罗斯拜瑞氏菌(*Roseburia intestinalis*)L1-82及其原噬菌体在小鼠肠道中的共进化进行了追踪研究。他们发现, Shimadzu噬菌体能够系统性地转变为更具杀菌能力的裂解型突变体, 这些突变体能有效杀死大多数易感的罗斯拜瑞氏菌, 从而改变了肠道内的微生物组成。Corbellino等人^[46]在最近的病例报告描述了一种使用体外分离的单一高效噬菌体(vB_KpnM_GF), 该噬菌体可以靶向清除肠道内的多重耐药克雷伯氏菌菌株, 清除率可达到100%。Disanayake等人^[47]研究表明, 针对大肠杆菌、沙门氏菌和李斯特菌的噬菌体混合物能在几乎不干扰菌群的情况下有效降低感染小鼠的致病性大肠杆菌O157:H7的菌株水平。

相比于烈性噬菌体, 肠道内大量噬菌体是以温和噬菌体状态存在的。“红皇后假说”正是用来解释二者之间的寄生关系。温和噬菌体可以将其基因组整合到宿主细菌的基因组中, 随宿主的复制而复制, 并不裂解细菌^[48]。噬菌体是不同细菌物种之间水平基因转移的重要载体, 可以通过转化或转导实现^[49]。Hsu等人^[50]利用基因工程改造温和噬菌体, 使其表达一种志贺毒素的转录抑制因子, 接着噬菌体通过“转化”的方式将该DNA片段注入到宿主大肠杆菌中, 从而使大肠杆菌能够中和毒力因子的表达, 减少肠道感染小鼠模型中志贺毒素的产生。 λ 噬菌体是一种经典的特化转导噬菌体, 通常将自己的基因组整合在宿主大肠杆菌基因组的半乳糖代谢和生物素生物合成操纵子之间, 偶尔发生的不精确基因组切除使得宿主DNA片段被误切并整合到

λ 噬菌体的基因组中, 并随后复制到所有生成的病毒粒子中, 促成肠道细菌之间代谢基因的水平转移^[51]。此外, 在金黄色葡萄球菌温和噬菌体和沙门氏菌噬菌体P22中观察到的横向转导允许高频宿主DNA的水平转移^[52,53], 说明噬菌体可以介导宿主DNA在细菌种群间发生水平转移, 从而使细菌群落的遗传多样性增加, 能够更好地适应环境的变化。

2 肠道微生物与宿主的互作关系

众多研究结果表明肠道菌群组成和结构受到多种因素影响, 具体包括宿主内在因素(如基因型、年龄和健康状态等)和外环境因素(如饮食、生活环境和药物使用等)。相比于外在因素, 内在因素及其变化是宿主与肠道微生物群互作的主要方式。Zhernakova等人^[54]发现宿主ABO位点与编码N-乙酰半乳糖胺(GalNAc)利用基因簇高度相关, 肠道中普氏粪杆菌(*Faecalibacterium prausnitzii*)拥有代谢GalNAc的具体通路。分泌型A型抗原是黏膜GalNAc的主要来源, 表明普氏粪杆菌等微生物在该类型的宿主肠道中生长得更好。随着年龄的增长, 肠道菌群的组成不断变化。相较于其他因素, 年龄对肠道菌群的影响是多方面的, 年龄的变化伴随着机体免疫、消化吸收能力、饮食和生活习惯的改变, 目前有研究者去除了其他混杂因素后, 发现多个与衰老过程显著相关的生物标记物, 如大芬戈尔德菌(*Finegoldia magna*)和齿双歧杆菌(*Bifidobacterium dentium*), 并且发现菌群对氨基酸利用会随着年龄的增加而改变^[55]。值得注意的是, 宿主与菌群间的关系是相互的, 通过改变肠道微生态也可实现对宿主健康的调节, 在此过程中, 肠道微生物间的互作关系扮演着重要角色, 其可以影响一些关键代谢物的产生(如短链脂肪酸、胆汁酸等), 从而实现与宿主互作并对宿主的机体代谢、生长发育和疾病进展产生影响(图2)。

2.1 菌群通过短链脂肪酸与宿主互作

短链脂肪酸是指六碳以下的脂肪酸, 主要包括乙酸、丙酸和丁酸, 肠道中短链脂肪酸的主要来源是微生物通过发酵膳食纤维而产生的。目前, 众多研究显示短链脂肪酸参与宿主机体多个代谢通路, 是肠道细菌与宿主互作的重要媒介。在肠道菌群研究中, 大量的研究报道了短链脂肪酸及其产生菌在肠道炎症^[56]、胃肠道疾病^[57]、神经系统疾病^[58]、代谢性疾病^[59]和慢性疲劳^[60]等非健康的肠道环境中显著下降, 而调节相关

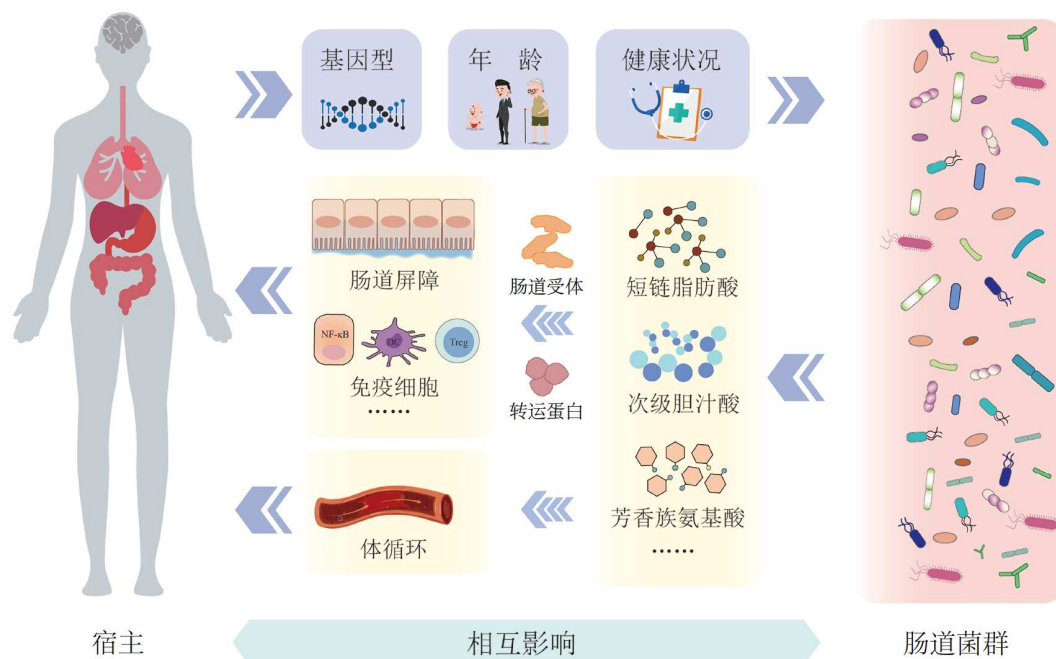


图2 (网络版彩色)宿主与肠道微生物相互作用

Figure 2 (Color online) The interaction between gut microbiome and host

菌种或补充短链脂肪酸可以缓解相应的症状。

乙酸盐及其相关代谢产物乙酰辅酶A(acetyl-coenzyme A, Acetyl-CoA)参与机体中多个代谢通路,包括能量生产、脂类合成和蛋白乙酰化等^[61]。产生IL-10的B细胞称为B10细胞,可以促进Treg细胞(regulatory T cells)分化和抑制辅助性T细胞(helper T cell, Th)1和Th17^[62], Daïen等人^[63]发现乙酸盐通过转化为乙酰辅酶A,然后通过为三羧酸循环(tricarboxylic acid cycle, TCA)和氧化磷酸化(oxidative phosphorylation, OXPHOS)提供燃料来增加能量可用性,以及通过乙酰辅酶A合成酶2(acetyl-coenzyme A synthetase 2, ACSS2)进行蛋白质乙酰化方式诱导B10细胞分化发挥抗炎作用。然而,在肥胖模型中的肠道菌群紊乱显著增加了肠道中乙酸的含量,进而激活了副交感神经系统,使得葡萄糖刺激的胰岛素分泌增加,导致食欲过盛、肥胖及相关症状^[64], Araujo等人^[65]也发现肠道中大肠杆菌产生的乙酸可以抑制肠细胞分泌乳糜微粒,促进脂质氧化,这主要是由于肠细胞吸收乙酸,将其代谢为乙酰辅酶A和单磷酸腺苷(adenosine monophosphate, AMP),随后上调了细胞脂质氧化的AMPK/PGC-1α/PPARα途径。此外,乙酸还可通过循环进入机体其他部位发挥有益作用, Song等人^[66]发现肠道中假长双歧杆菌分泌的乙

酸可以通过静脉到达肝脏,与肝细胞G偶联蛋白受体(G protein-coupled receptor, GPR)43结合,进而抑制IL-6/JAK1/STAT3信号通路,阻止非酒精性脂肪性肝病相关的肝癌进展。

肠道中丙酸主要通过琥珀酸通路产生,在这过程中,拟杆菌门的细菌发酵碳水化合物或厚壁菌门的细菌通过乳酸或琥珀酸代谢产生丙酸^[67]。丙酸参与调节机体黏膜免疫、调整食欲、抗炎、降胆固醇和抗癌等作用^[68-70]。肠道中多形拟杆菌是丙酸产生的关键菌种,其中mutA-和scpa2编码的甲基丙二酰辅酶A变位酶(methylmalonyl coenzyme amutase, MCM)是负责丙酸生产的操作基因操纵子,多形拟杆菌的甲基丙二酰辅酶A变位酶可以通过GPR41增加肠道丙酸水平并促进肠上皮细胞分化,从而调节肠黏膜屏障功能^[67]。同时, Duan等人^[71]也发现海藻糖可以促进肠道干细胞的增殖和分化,这过程主要与其增加了肠道中丙酸产生菌嗜黏蛋白阿克曼氏菌(*Akkermansia muciniphila*)的丰度及丙酸含量相关。此外,在婴儿早期营养中,丙酸也发挥着重要的作用。婴儿早期的营养不良是公认的后期哮喘发展的风险因素,母体肠道中的丙酸盐通过ADAM10促进树突状细胞生长因子Fms样酪氨酸激酶3配体(Fms-like tyrosine kinase 3 ligand, Flt3L)释放,帮助

促进子代树突状细胞分化,进而降低孕期营养不良对后代哮喘等疾病的影响^[72]。

丁酸的产生途径是比较多样化的,主要被肠道上皮吸收,作为肠黏膜的能量来源参与体内众多代谢通路。在所有的短链脂肪酸中,丁酸是被广泛证明的免疫调节剂^[73-76]。丁酸可以与GPR41、GPR43和GPR109A进行结合,进而可诱导NOD样受体热蛋白结构域相关蛋白3(NOD-like receptor protein 3, NLRP3)炎性小体的活化和结肠上皮细胞IL-18的分泌,促进中性粒细胞向炎症部位募集,增强叉头盒蛋白P3(forkhead box protein P3, FOXP3)调节性T细胞的分化和抑制功能等^[77],丁酸盐还可通过增加组蛋白乙酰化和增加开放染色质的数量,影响肠上皮细胞、巨噬细胞、树突状细胞和淋巴细胞,特别是Treg细胞的基因表达,进而调节机体免疫^[78-80]。在肠屏障修复方面,丁酸不仅可以调节肠道干细胞增殖分化,还可增加上皮细胞紧密连接蛋白(claudin 1、claudin 3、claudin 4和occludin)^[81,82]的表达和增加肠上皮细胞的耗氧量等方式促进肠道屏障功能^[83]。此外,丁酸在肝肾、神经系统^[84]和生殖道等疾病中的作用也被广泛报道,例如丁酸盐介导的抑制组蛋白去乙酰化酶1(histone deacetylase 1, HDAC1)和上调肿瘤抑制因子RAP1鸟嘌呤核苷酸酶激活蛋白(RAP1 GTPase activating protein, RAP1GAP)可以抑制小鼠子宫内肌瘤的进展和人子宫内肌瘤细胞的生长^[85]。

2.2 菌群通过胆汁酸代谢与宿主互作

胆汁酸是肝脏胆固醇代谢的最终产物,初级胆汁酸在肝脏中产生,与牛磺酸和甘氨酸结合后分泌到肠道,在肠道由肠道微生物通过胆汁酸盐水解酶(Bile Salt Hydrolase, BSH)转化为次级胆汁酸。众多研究表明,肠道微生物可以通过次级胆汁酸代谢与宿主产生互作。细菌代谢产生的次级胆汁酸可以作为信号分子,通过与特异性受体,如法尼脂类X受体(Farnesoid X receptor, FXR)和G蛋白偶联膜受体5(G protein-coupled bile acid receptor 5, TGR5)结合,介导宿主代谢和免疫的各种途径,或作为抗菌化合物,通过选择性重塑肠道菌群组成间接影响宿主生理^[86,87]。

目前研究较多的次级胆汁酸主要有脱氧胆酸(deoxycholic acid, DCA)和石胆酸(lithocholic acid, LCA),这两类次级胆汁酸也是肠道微生物组最丰富的代谢产物,不同次级胆汁酸在健康中的作用存在较大差异。Jin等人^[88]发现脱氧胆酸可以促进人胃黏膜上皮

细胞(gastric epithelial cells, GES-1)细胞增殖,增加促炎细胞因子和肠道标志物表达、减少细胞凋亡并通过TGR5促进信号传导及转录激活蛋白3(signal transducer and activator of transcription 3, STAT3)磷酸化,后者结合到Kruppel样转录因子5(Kruppel-like factors5, KLF5)基因启动子上激活KLF5表达,从而促进肠化生的发生发展;Song等人^[89]也报道了高脂饮食通过改变小鼠肠道菌群增加了粪便中脱氧胆酸的含量,进而诱导了Apcmin/+小鼠肿瘤细胞增殖及上皮间质转化,驱动血管生成拟态形成并伴随血管内皮生长因子受体2(vascular endothelial growth factor receptor, VEGFR2)激活,促进肿瘤发生。相对于脱氧胆酸来说,石胆酸及其衍生物在大多数的报道中则是具有积极作用。据报道,百岁老人肠道中的石胆酸衍生物大量富集,主要产生者为拟杆菌目细菌^[90],石胆酸衍生物可以通过抑制肠道有害菌,调节肠道微生态助力长寿。石胆酸也可激活TGR5发挥抗炎作用,并抑制结肠中M1巨噬细胞的极化来缓解结肠炎的进展^[91],还可通过提高机体对维生素A和维生素D的吸收,提高卵母细胞质量、胚胎发育和精子形成^[92,93]。

近年来,科学家们鉴定出了很多新型次级胆汁酸。克里斯滕森氏菌(*Christensenella minuta*)能生成一类以3-O-酰基化取代为特征的新型次级胆汁酸,如3-O-乙酰/丙酰/丁酰基-胆酸,其是FXR拮抗剂,可以调控肠FXR-肠肝信号轴改善宿主代谢^[94]。异脱氧胆酸(Iso-deoxycholic acid, isoDCA)在肠内含量较高,并且通过与树突状细胞中的FXR互作,促进结肠中的外周调节性T生成^[95]。微生物偶联胆汁酸(microbially conjugated bile acids, MCBAs)是在博尔特梭菌(*Enterocloster boltea*)等微生物将在胆酸主链上与苯丙氨酸、亮氨酸和酪氨酸进行偶联得到的,微生物偶联胆汁酸可能参与机体疾病的发生发展,但具体作用及分子机理仍需进一步探究^[96]。

2.3 菌群通过芳香族氨基酸代谢与宿主互作

除了短链脂肪酸和胆汁酸代谢外,氨基酸代谢也被认为是细菌与宿主互作的重要通路,尤其是色氨酸和苯丙氨酸等芳香族氨基酸。这些芳香族氨基酸被肠道微生物利用代谢产生吲哚和酚类化合物等多种代谢产物,调节机体免疫和代谢。

大多情况,芳香族氨基酸的代谢产物被认为通过抗炎和神经调节等方式对健康发挥着积极作用。Laur-

sen等人^[97]通过对生命早期肠道芳香族氨基酸分解代谢产物分析发现, 芳香族乳酸主要由双歧杆菌属产生, 芳香丙酸主要由厌氧消化链球菌产生, 色胺主要由瘤胃球菌属产生。其中苯乳酸(phenyllactic acid, PLA)被认为与机体免疫相关, 可以通过增加小肠上皮细胞中过氧化物酶体增殖物激活受体 γ (peroxisome proliferator-activated receptor γ , PPAR- γ)的含量, 保护免受抗生素和高脂饮食引起的代谢功能障碍的影响^[98]; 吲哚丙酸(indolepropionic acid, IPA)通过增加Tcf7基因超级增强子上的H3K27乙酰化修饰, 调节CD8⁺ T细胞干性, 增加肿瘤内的前体耗竭CD8⁺ T细胞(Tpex, 响应抗PD-1治疗的重要T细胞亚群)并促进其分化为效应T细胞^[99]。吲哚-3-甲醛(indole-3-carboxaldehyde, I3A)是色氨酸经肠道菌群代谢后的吲哚衍生物, 其可通过激活肠道AhR/IL-10/Wnt信号通路和增加有益菌丰度, 从而促进Lgr5⁺肠干细胞的增殖和分化, 实现对肠道屏障功能的维持^[100]。在神经调节方面, Sugiyama等人^[101]发现厚壁菌门中的5个主要属(*Blautia*、*Clostridium*、*Enterococcus*、*Ruminococcus*和*Tyzzelerella*)具有通过芳香氨基酸脱羧酶(aromatic amino acid decarboxylase, AADC)的作用大量产生芳香胺的能力。芳香胺广泛存在于肠道中, 其中酪胺、色胺和苯乙胺是典型的微量胺, 即使很少量也可以影响神经传递^[102,103], 例如诱导多巴胺, 血清素和去甲肾上腺素等神经递质的外排^[104]。

然而, 也有部分结果报道芳香族氨基酸代谢产物对健康有一些负面作用。肠道干细胞(intestinal stem cells, ISCs)是肠上皮细胞的制造工厂, 是肠道上皮细胞更新、补充新细胞和应对肠道屏障损伤修复的主要来源, 在维持机体肠道稳态和功能方面发挥着重要的作用。 α -2A-肾上腺素能受体(α -2A adrenergic receptor, ADRA2A)是ISC中高表达的G蛋白偶联受体, 而酪胺是 α -2A-肾上腺素能受体的微生物配体, 主要由肠道中肠球菌属的细菌(如粪肠球菌)产生。在炎症性肠病中, 肠球菌属的细菌通过代谢产生酪胺参与肠道干细胞上的 α -2A-肾上腺素能受体激活, 下调cAMP信号, 抑制肠道干细胞增殖和肠上皮修复, 从而加剧结肠炎^[105]。同时, 肠道微生物群对芳香氨基酸的代谢产生了可能与心脏代谢疾病相关的代谢物, 例如苯乙酰谷胺(phenylacetylglutamine, PAGln), 一种苯丙氨酸(phenylalanine, Phe)衍生的肠道微生物代谢物, 可通过肾上腺素受体信号通路影响心血管疾病。肠道菌群也可将酪氨酸和色氨酸分解为对甲酚硫酸盐和硫酸吲哚酚, 这两种物质与重

大心血管不良事件风险(major adverse cardiovascular events, MACE)、全因死亡率相关^[106]。

2.4 菌群与宿主其他方面的互作关系

除了上述几种代谢通路外, 肠道菌群也可通过其他重要代谢物实现与宿主的交流。尿酸在机体健康中也扮演着重要的角色, 血清尿酸的升高是高尿酸血症和痛风的重要危险因素。肠道细菌可以通过降解外源核苷、抑制黄嘌呤氧化酶活性和调节肠上皮尿酸转运蛋白直接参与机体尿酸代谢过程^[107~109]。Liu等人^[109]发现肠道中大量厌氧菌可以代谢尿酸, 将其转化为黄嘌呤、乳酸或乙酸和丁酸。Xu等人^[110]发现高尿酸血症患者中另枝菌属(*Alistipes indistinctus*)的丰度显著降低, 其代谢产生的马尿酸通过增强过氧化物酶体增殖物激活受体 γ 与ATP结合盒亚家族G成员2(ATP binding cassette subfamily G member 2, ABCG2)启动子的结合, 从而促进肠道尿酸排泄。此外, 氧化三甲胺(Trimethylamine N-oxide, TMAO)是一种小分子无色氧化胺, 来源于肠道菌群对胆碱、甜菜碱及肉毒碱的代谢, 其是心血管疾病公认的危险因素^[111]。已经有越来越多的研究结果显示TMAO在其他疾病进程中的作用。在糖尿病中, TMAO可直接降低小鼠或人类的小鼠胰岛素瘤细胞(mouse insulinoma pancreatic beta cell line, MIN6)和原代胰岛的葡萄糖刺激胰岛素分泌(glucose-stimulated insulin secretion, GSIS), 并通过NLRP3炎症小体相关的细胞因子抑制钙转换并诱导Serca2丢失, 进而损害 β 细胞功能^[112]。先兆子痫(preeclampsia, PE)是怀孕常见的并发症, TMAO通过调节炎症和氧化应激相关的信号通路, 影响血管内皮细胞的迁移和血管生成, 以及滋养层细胞的迁移和侵袭, 促进先兆子痫的发展^[113]。

3 总结与展望

在过去的几十年里, 我们对肠道微生物与健康间潜在关系的认识取得了显著进展, 明确了其在宿主免疫、代谢和疾病的发生发展中发挥着重要的作用, 也初步解析了部分微生物影响宿主健康的具体分子机制。然而, 该领域仍然存在许多为未明确的问题需要进一步探索和深入挖掘。在肠道环境中, 微生物通过密切的互作网络进行沟通和交流, 某个微生物物种的增加或减少并不一定直接对应某些代谢物的变化或宿主健康状态的变化, 在这中间应该有着微生物间互作关系的变化和肠道微生态整体的调控。对肠道微生物间网络

关系的探究是一个复杂且具有挑战性的研究领域, 目前专门针对肠道微生物间相关关系的研究仍处于起步阶段, 仅明确了一些简单的一对一关系, 并非微生物间的互作网络, 研究的深度和广度有限, 有待于更深入地

研究. 未来的研究应当进一步以肠道环境为背景, 结合培养组学和人工智能等手段, 深入挖掘肠道微生物间的互作关系, 及其与功能性代谢物和机体健康间的潜在关系.

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Summary for “肠道微生物间互作及其代谢物发挥作用的研究进展”

Interactions between gut microorganisms and the role of their metabolites in host health

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Over the past few decades, significant progress has been made in understanding the potential relationships between gut microbes and health, and clarifying that the intestinal tract is an intact micro-ecosystem with highly complex interactions between gut microbes. At present, studies focusing specifically on the relevant relationships between gut microorganisms are still in their infancy, and only some simple one-to-one relationships, rather than networks of interactions between microorganisms, have been elucidated. The present review summarized the interactions between gut microorganisms, as well as the pathways by which they interact with the host via metabolites. Among the relationships between gut microorganisms, bacteria are one of the most studied microorganisms in the ecology of intestinal tract communities, and the main interactions among gut bacteria are neutral, symbiotic, competitive, and predatory. Neutral or beneficial interactions can be defined as symbiosis, and mutualistic symbiosis is a special mechanism of microbial interactions in which some microorganisms are able to provide each other with nutrients or survival conditions needed by the other and thus mutually benefit, e.g. *E. coli* in the gut ferment glucose to excrete organic acids to provide a carbon source for *R. palustris*, while *R. palustris* converts N_2 to NH_4^+ to provide an essential nitrogen source for *E. coli*. Resistance interactions (including competition, mutualistic symbiosis and predation) also occur among gut bacteria, where they compete for nutrients and ecological niches, produce inhibitory substances (e.g. antibiotic bacteriocins) or invade host cells to cause host death and thereby exert an inhibitory effect on other bacteria. *Candida* and *Saccharomyces* dominate the human gut fungal community, and the relationships between the gut fungal and bacteria are mainly cooperative and antagonistic, e.g. *C. tropicalis* can form biofilms with pathogenic bacteria (such as *E. coli* and *S. marcescens*) to protect them from immune cells, and *L. plantarum* can inhibit *C. albicans* abundance in the gut by producing beneficial metabolites. The relationship between gut bacteria and phages is parasitic and can be characterized by “kill the winner” kinetics and the “red queen hypothesis” depending on the type of phage. The relationship between host and gut microbes is mainly mutualistic, with the host providing a favourable ecological environment for the growth of gut microbes and the gut microbes contributing to the health of the host through a variety of metabolic responses. In the process of microbial regulation of organismal health, microbial metabolites are the main medium. Key metabolites, such as SCFAs, secondary bile acids and aromatic metabolites, can stimulate corresponding immune cells, and regulate the intestinal barrier effect via intestinal receptors and transport proteins, and can also dialogue directly with the host via the circulation, ultimately playing an important role in the host’s nutrient absorption, metabolism, immune system development and pathogen defense. Overall, the regulation of health by gut microbes should be the result of a network of interactions, rather than changes in the levels of individual microbes in the gut. The interactions between gut microbes and their potential relationship with functional metabolites and health should be further explored by combining culture genomics and artificial intelligence.

gut microbes, metabolites, interactions, host health

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