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·综述·

精氨酸在口-肠菌群中的代谢及其稳态调控作用的研究进展

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【摘要】 菌群失衡会导致微环境失调，引发龋病、炎症性肠病、肥胖和糖尿病等局部或全身性疾病。菌群失衡主要表现为代谢过程及产物的紊乱，精氨酸在宿主和菌群的多种代谢过程中发挥重要作用。本文拟从精氨酸在口-肠菌群中的代谢及其稳态调控作用入手，探讨其在菌群失衡相关疾病中的潜在治疗价值。干预或调控宿主微生物的组成或功能有望恢复宿主和微生物的稳态，精氨酸具有极高的临床应用潜能。精氨酸参与调控变异链球菌和血链球菌的相对丰度，有望降低龋病的发病风险。精氨酸代谢参与调控厚壁菌门与拟杆菌门的相对丰度，在炎症性肠病以及肥胖的改善中可以发挥重要作用。精氨酸及其代谢产物多胺在酮症酸中毒倾向性糖尿病的治疗中也有良好的治疗前景。虽然精氨酸在口腔疾病、肠道疾病及代谢相关疾病的治疗中发挥了重要作用，但其是否发挥直接作用仍未明确，其具体作用机制也需进一步阐明。此外，目前尚无研究证实其临床应用的最适浓度，掌握合适的精氨酸剂量以精确调控菌群的组成，避免其产生副作用也是未来进一步研究的方向。

【关键词】 精氨酸；口-肠菌群；代谢；稳态调控；菌群失调；生物多样性；益生元；龋病；炎症性肠病；代谢紊乱性疾病
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Research progress on the metabolism and homeostatic regulation of arginine in oral-intestinal flora

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【Abstract】 Dysbiosis can cause microenvironmental dysregulation, which can further lead to local or systemic diseases, such as caries, inflammatory bowel disease, obesity, and diabetes. Dysbiosis is primarily manifested as the disturbance of metabolic processes and products. Arginine plays an important role in various metabolic processes and homeostasis of the microbial flora and the host. This study aims to explore the potential therapeutic value of arginine and its metabolism and homeostasis regulation in diseases associated with oral - intestinal dysbiosis. Host and microbial homeostasis can be restored by regulating the composition or function of host microbiota, and arginine has been found to exhibit significant clinical potential in restoring host microbiota composition and function. For example, arginine can reduce the risk of caries by regulating the relative abundance of *Streptococcus mutans* and *Streptococcus sanguineus*. Additionally, arginine metabolism may play a therapeutic role in inflammatory bowel disease and obesity by regulating the relative abundance of Firmicutes and Bacteroidetes. In addition, supplementation of arginine and its metabolite polyamine has clinical

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prospects in the treatment of diabetic patients with ketoacidosis. Although studies have demonstrated the therapeutic role of arginine in oral, intestinal, and metabolism-related diseases, the specific mechanism is yet to be explored. In addition, further research is required to determine the optimal clinical dosage of arginine that can maintain microbiota homeostasis without causing any side effects.

【Key words】 arginine; oral-intestinal flora; metabolism; homeostatic regulation; dysbacteriosis; biodiversity; prebiotics; caries; inflammatory bowel disease (IBD); metabolism disorder disease

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随着高通量测序等技术的发展，有关菌群与宿主间相互作用的研究取得了巨大进展[1]。生理状态下，菌群与宿主处于动态平衡状态[2]。菌群失衡会破坏稳态，导致微环境失调，继而引发局部或全身疾病。菌群失衡主要表现为代谢过程及产物的紊乱[3-5]。精氨酸在宿主和菌群的多种代谢过程中发挥重要作用，它可以通过改变菌群的生物多样性增强宿主维持稳态的能力，是一种常见的益生元[6-7]。健康状态下，人体有足够的精氨酸。但若出现低精氨酸血症等稳态失衡的情况，精氨酸将无法满足宿主和菌群的代谢需求进而引发多种疾病[8-9]。近年来多项研究表明，通过向菌群补充精氨酸或提高其对精氨酸的代谢活性有助于恢复宿主稳态，精氨酸可以作为连接菌群和宿主稳态的中介因子[10-13]。因此，本文拟从精氨酸在口-肠菌群中的代谢及其稳态调控作用入手，探讨其在菌群失衡相关疾病中的潜在治疗价值。

1　精氨酸在宿主细胞及菌群中的代谢机制及产物

人体内，细胞与菌群对精氨酸的代谢方式和终末产物不尽相同（图1）。宿主细胞对精氨酸的代谢主要由一氧化氮合成酶（nitric-oxide synthase, NOS）和精氨酸水解酶（arginase, ARG）承担。NOS根据不同的细胞定位可以分为3个亚型：内皮细胞型，神经细胞型和诱导型。尽管在人体内的分布不同，各亚型的NOS均可利用精氨酸作为底物产生NO并在体内发挥重要的调控作用[14-15]。例如，巨噬细胞等免疫细胞在炎症因子的刺激下，可以利用神经细胞型产生NO等活性氧分子（reactive oxygen species, ROS）继而在免疫应答中承担重要角色。又如，靶向补充精氨酸可以稳定内皮细胞型并产生NO，提高NO生物利用度并达到扩张血管和抗血栓等作用。

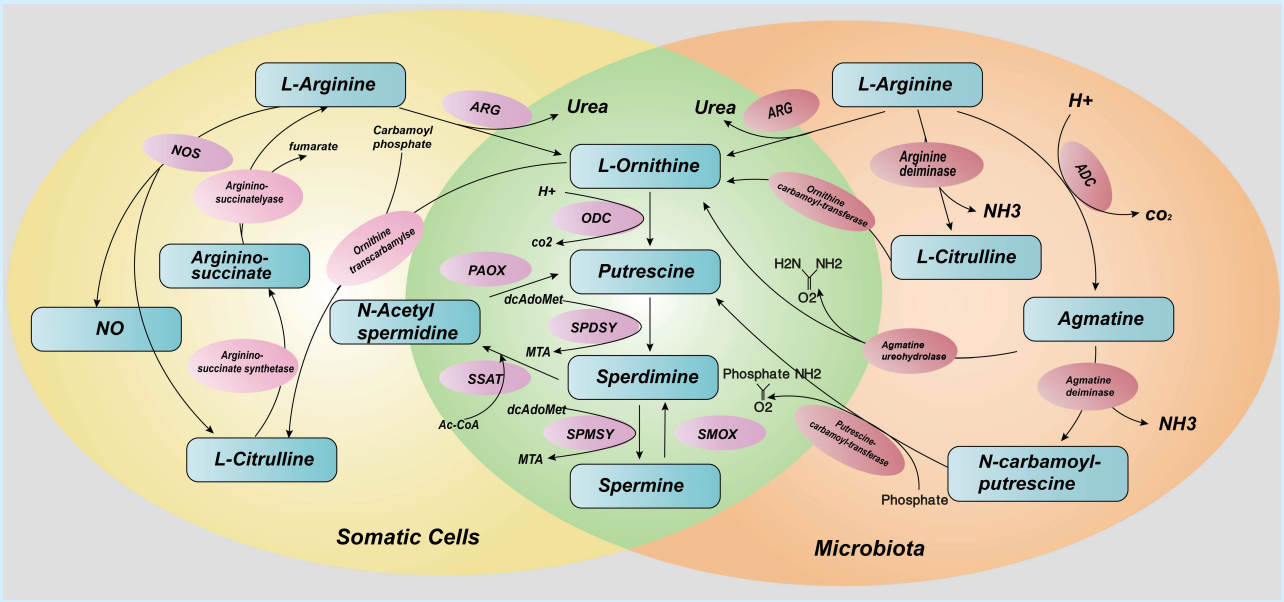
不同于NOS仅存在于宿主细胞，ARG是宿主细胞和菌群代谢精氨酸的共有途径。ARG可以将精氨酸水解为鸟氨酸和尿素，鸟氨酸是腐胺、精胺以及亚精胺等聚胺（polyamine）的重要前体物质[16]。聚胺广泛地参与在核苷酸、蛋白质的合成中，是维持生命活动的重要物质。例如，聚胺能够参与DNA结构的调节，介导染色质重塑，促进与抑制基因转录相关的染色质的缩合等[17]。

除了上述途径外，细菌还可以通过产生精氨酸脱羧酶（arginine decarboxylase, ADC）的方式将精氨酸转化为聚胺，且人体内聚胺的合成主要来源于肠道菌群通过ADC的途径合成[18]。此外，部分细菌可利用其特有的精氨酸脱亚氨酶（arginine deiminase）将精氨酸代谢为瓜氨酸，并进一步转化为鸟氨酸的方式参与聚胺类物质的合成过程[19-20]。

2　精氨酸代谢对菌群的调控

精氨酸及其代谢产物是维持生命活动的重要物质，精氨酸代谢是菌群代谢活动的重要组成部分。精氨酸代谢对菌群的调控作用最早可以追溯至新生儿肠道菌群定植的过程。研究显示，CD71+有核红细胞（erythroblast）来源的ARG可通过抑制新生儿的固有免疫介导肠道微生物的定植[21-22]。尽管这种免疫抑制有可能引发细菌移位，但鼠模型的研究结果显示，精氨酸还可以通过NO依赖的方式调节肠道黏膜的通透性，继而减少细菌移位的可能性，继而代偿了感染发生的风险[23-24]。

除了细菌的定植过程外，成熟的菌群同样受到精氨酸代谢的调控。精氨酸可以调控菌群内物种的组成比例。有研究显示，精氨酸可以选择性地降低口腔内变形杆菌的数量，增加拟杆菌、厚壁菌以及梭杆菌的数量[25]。然而，也有文章指出日常饮食摄入的精氨酸主要在增加拟杆菌的同时减少厚壁菌。尽管精氨酸对菌群内物种组成改变的具体情况尚未完全明确，但越来越多证据指出，精氨酸可以选择性地上调或下调菌群中的某些特定物种。例如，精氨酸可以上调口腔菌群中的血链球菌，并下调变异链球菌的数量[26]。



NOS: nitric-oxide synthase; ARG: arginase; PAOX: polyamine oxidase; ODC: ornithine decarboxylase; SPDSY: spermidine synthase; SSAT: Spermidine N1- acetyltransferase; SPMSY: spermine synthase; SMOX: spermine oxidase; ADC: arginine decarboxylase; dcAdoMet: S-adenosylmethionine decarboxylase; MTA: methylthioadenosine; Ac-CoA: Acetyl-coenzymeA

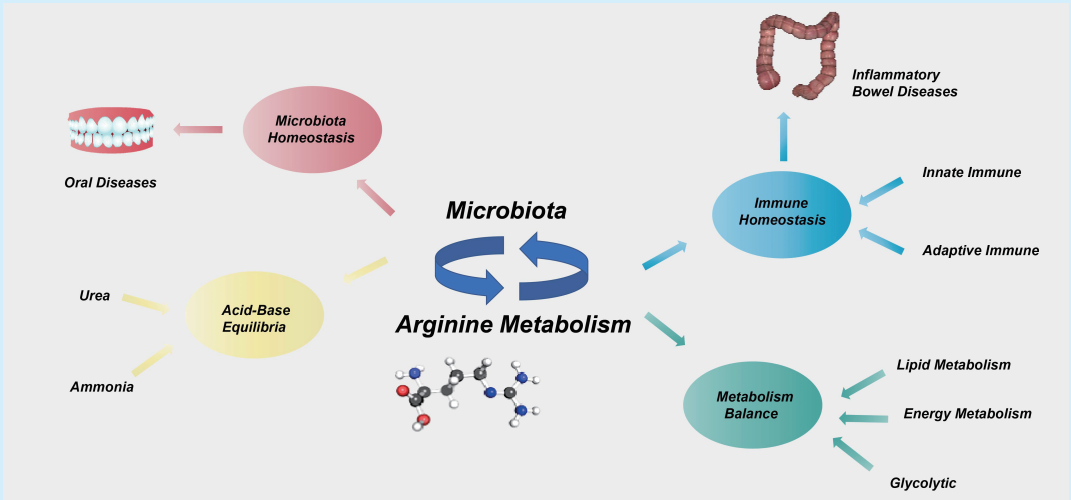
Figure 1 Arginine metabolism in the host and bacterial cells

图1　细胞和细菌对精氨酸的代谢过程

此外，精氨酸还可影响菌群的三维结构。研究表明，低剂量的精氨酸即可显著影响口腔菌群生物膜量以及厚度等。例如，有学者在使用精氨酸处理戈登链球菌的生物膜，通过转盘流变仪测定后发现，精氨酸干预后的生物膜出现了三维结构上的分离和重排，继而导致其机械完整性受到了破坏，抗剪切力能力下降，从而更容易在外力的作用下从牙齿表明脱落[27-28]。尽管具体的作用机制尚未完全清楚，但可能与精氨酸可以调节细菌间信号交流系统，继而减少不可溶性细胞外多糖（exopolysaccharides，EPS）的产生有关[29]。EPS是细菌形成生物膜的重要组分，EPS组分的改变会影响生物膜的最终形态[30]。

3　精氨酸代谢在宿主局部或全身疾病中的作用

如图2所示，微生物涉及的精氨酸代谢参与宿主机体稳态的维持[31]，具体表现如下：



The disorder of microbiome homeostasis, acid-base equilibria, immune homeostasis and metabolism balance caused by the imbalance of arginine metabolism can lead to oral diseases, inflammatory bowel disease, obesity, diabetes and other diseases

Figure 2　Association between microbial arginine metabolism and host homeostasis

图2　微生物涉及的精氨酸代谢与宿主体内平衡的关系

3.1 龋病

口腔菌群的失衡与龋病等口腔疾病的发生密切相关。近年来有研究显示，口腔菌群中变异链球菌和血链球菌的相对丰度比与龋病的发生发展之间存在一定的关联。体外实验结果证实，精氨酸可以选择性增加血链球菌的相对丰度，从而降低龋病的发生风险[32]。另有临床实验证实，在牙膏中添加精氨酸给高龋患者使用两个星期后，患者口腔菌群中的变异链球菌显著减少而血链球菌的丰度显著增多，有效降低了龋病的发生风险[33]。尽管精氨酸调控口腔菌群组成的具体机制尚未完全清楚，但诸多证据表明其可能与微生物的精氨酸脱亚氨酶系统（arginine deiminase system, ADS）有关。ADS主要将精氨酸脱氨形成瓜氨酸和尿素等碱性物质，是口腔内维持酸碱平衡的重要手段[34]。研究显示，相较于高龋人群，健康人群口腔来源的菌群中*arcA*和*ureC*等ADS相关基因的丰度更高[35]。此外，ADS系统还被证明可以抑制口腔菌群中部分产酸耐酸菌的蔗糖代谢活性[36]。因此，精氨酸在口腔疾病尤其是龋病等涉及菌群失衡相关的疾病治疗中具有重要价值。

3.2 炎症性肠病

炎症性肠病（inflammatory bowel disease，IBD）是一类累及回肠、直肠、结肠等肠道多部位的特发性炎症。IBD依照发病部位和症状主要可分为溃疡性结肠炎和克罗恩病。尽管确切的发病机制尚未完全明确，但诸多证据表明，宿主免疫及肠道菌群在疾病的发生发展中发挥了重要作用[37-41]。近年来的研究显示，精氨酸及其代谢可能成为治疗IBD的重要靶点[42-45]。小鼠IBD模型试验结果显示，相较于野生型小鼠，Arg1基因敲除的小鼠在IBD造模后具有更加良好的预后[10]。敲除其他精氨酸代谢相关的基因（Arg2或Nos2）可以达到相同的效果。敲除了精氨酸代谢相关的基因后，小鼠肠道菌群的组成同样产生了变化，主要表现为厚壁菌门的相对丰度增加，而拟杆菌门的相对丰度降低。

尽管尚不清楚菌群组成的改变与IBD预后的改善之间是否存在因果关联，但有证据显示，肠道菌群中的厚壁菌门与拟杆菌门的丰度比值与IBD存在重要关联。在关于IBD患者肠道菌群的研究中发现，其肠道菌群的特征主要表现为厚壁菌门的相对丰度减少，拟杆菌门相对丰度增加[39]。体内外研究证实，厚壁菌门中某些成员，如普拉梭菌（*Faecalibacterium prausnitzii*）可以通过增加IL-10的分泌，并减少IL-12和IFN-γ的方式发挥抗炎能力，继而维护肠道免疫稳态，减轻IBD等肠道炎症的症状[46]。因此，通过调控精氨酸代谢的方式改变肠道微生物的组成具有临床治疗IBD的潜在应用价值，但具体机制及效果仍有待进一步的研究和证实。

3.3 代谢紊乱性疾病

肥胖如今已被认为是一类重大公共健康问题。特别是在过去几十年，肥胖的发病率持续以惊人的速度上升，全世界近20亿成年人被认为超重，其中50%被归类为肥胖[47]。尽管导致肥胖发生的原因较为复杂，但肠道菌群的紊乱发挥了重要作用[48-49]，通过多种方式干预肠道菌群的改变已成为治疗或预防肥胖发生的重要靶点[50-52]。

越来越多的证据显示，肥胖的发生与肠道菌群中厚壁菌门的相对丰度增加、拟杆菌门相对丰度降低有关[53]。这可能是由于相较于拟杆菌门，厚壁菌门的成员拥有更强的代谢碳水化合物和脂类的能力[54]。考虑到精氨酸具有选择性增加肠道菌群中拟杆菌门相对丰度的能力，其已被认为具备作为治疗肥胖的潜在价值，并因此受到了广泛的关注[55]。研究显示，给小鼠口服精氨酸可以有效减少其体内白色脂肪组织，改善棕色-白色脂肪组织[55]。而在临床研究中发现，给肥胖症患者每日补充精氨酸后，患者的体重、腰围及脂肪组织的量和分布均有明显改善[56]。

糖尿病是另一类重要的代谢紊乱相关疾病。酮症酸中毒倾向性糖尿病（ketosis-prone diabetes, KPD）是一种特殊的糖尿病亚型。尽管不存在胰岛β细胞的自身免疫，血糖长期稳定，但患者仍会出现糖尿病酮症酸中毒症状[57]。研究显示，KPD患者多存在机体精氨酸含量不足[58]。体外研究显示，精氨酸可以有效促进葡萄糖刺激的胰岛β细胞胰岛素分泌，因此精氨酸含量的不足可能是导致KPD患者胰岛β细胞分泌胰岛素功能障碍的原因[59]。此外，精氨酸代谢的终末产物多胺同样被认为与KPD的发生有关。由于胰岛中的多胺主要分布在胰岛β细胞的分泌颗粒中，因此被认为其参与了胰岛素前体的合成和胰岛素的分泌[60]。在多胺分解酶过表达的模型鼠中可观察到胰岛中的多胺含量显著下降以及受损的胰岛素分泌。因此，补充精氨酸或其相关的代谢产物可能有助于临床治疗此类糖尿病患者并预防酮症酸中毒的发生。

4 展 望

虽然精氨酸在口腔疾病、肠道疾病及代谢相关疾病的治疗中发挥了重要作用，但要进一步大规模推广使用仍有一些亟待解决的问题。首先，精氨酸治疗上述疾病的具体机制尚未完全明确。现阶段，还无法确定精氨酸是否是通过调控菌群进而发挥出治疗效果。尽管在诸多实验中观察到了给予患者精氨酸后，患者口腔或肠道菌群的改变伴随有临床症状的缓解。但缺乏相关证据证明这种菌群的改变是否先于临床症状的缓解。菌群的改变有可能是受到疾病相关因素的影响而发生了改变，而并非是导致疾病症状缓解的直接原因，二者之间的因果关系仍有待进一步的证明。此外，目前尚无研究指出临床应用精氨酸治疗微生物失衡相关疾病的最适浓度。精氨酸可以选择性改变菌群中某些特定物种的丰度，但这些物种在不同的疾病中扮演的角色极为复杂。如厚壁菌门的某些成员在IBD等疾病中承担着抑制炎症因子分泌和激活的作用，但在肥胖等疾病中又会造成过多的白色脂肪组织堆积。因此，掌握合适的精氨酸剂量以精确调控菌群的组成，避免其产生副作用也是未来进一步研究的方向。

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