

# 病原细菌氨基酸代谢与其致病机制关系研究进展

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**摘要:** 氨基酸是生命体的重要组成成分和营养物质。许多研究表明, 病原细菌的氨基酸代谢在其致病过程中发挥着关键作用。本文综述了不同氨基酸在促进病原细菌致病过程中的作用, 重点阐述了肠沙门氏菌利用天冬氨酸实现在结肠炎肠道中的定殖和扩散, 以及支链氨基酸通过全局转录调控因子 CodY 间接调控金黄色葡萄球菌等病原细菌毒力的机制, 并简要概括了其他氨基酸代谢在病原细菌感染进程中的重要作用。深入研究氨基酸代谢在病原细菌致病过程中的调控作用, 有助于深化对其致病机制的认识, 进而为开发新的抗菌策略提供理论依据。

**关键词:** 病原细菌; 氨基酸代谢; 致病机制; 天冬氨酸; 支链氨基酸

## Linking amino acid metabolism to pathogenicity in pathogenic bacteria: current perspectives

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**Abstract:** Amino acids serve as indispensable components and nutrients for living organisms, while recent studies have revealed that amino acid metabolism in pathogenic bacteria plays a pivotal role in their pathogenic processes. This review summarizes current research on the roles of different amino acids in facilitating the pathogenicity of pathogenic bacteria. Specifically, we

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highlight how *Salmonella enterica* utilizes L-aspartate to achieve colonization and dissemination within the inflamed intestine, and how branched-chain amino acids indirectly regulate the virulence of *Staphylococcus aureus* via the global transcriptional regulator CodY. Additionally, we briefly outline the vital roles of amino acid metabolism throughout the infection processes of pathogenic bacteria. In-depth research into how amino acid metabolism promotes pathogenic processes will deepen our understanding of the underlying mechanisms and provide a theoretical basis for developing novel antibacterial strategies.

**Keywords:** pathogenic bacteria; amino acid metabolism; pathogenic mechanism; aspartate; branched-chain amino acids

细菌感染不仅是感染性疾病发生的直接诱因，也是非感染性疾病病情恶化的难控性危险因素。尽管抗生素的广泛使用显著降低了细菌感染相关疾病的死亡率，但随之产生的抗生素耐药性使得病原细菌感染始终是全球医疗和公共卫生领域面临的重要挑战。2024年，世界卫生组织更新了可能引发未来全球大流行的优先病原体清单，新增了5种高威胁病原细菌<sup>[1]</sup>；同年，世界卫生组织还专门发布了值得关注的耐药细菌清单，以指导全球病原细菌感染疾病的防控研发工作<sup>[2]</sup>。这些举措表明，深入研究细菌致病机制并优化应对策略仍是医疗和公共卫生领域的迫切需求。

氨基酸作为细菌生长繁殖的关键碳源和氮源，不仅负责合成细菌中各种功能性多肽或蛋白质，还直接影响细菌在宿主体内的增殖以及毒力机制的维持。与人体相比，细菌的氨基酸代谢通路高度复杂且多样化，其通路中的特异性酶及代谢产物在细菌基因表达调控网络中扮演着多重角色。不同细菌种群间氨基酸代谢通路的差异，不仅反映了它们适应宿主体内不同限制性环境的能力，也与其致病过程密切相关。尽管早期关于细菌自身氨基酸代谢与致病性之间关联的研究相对匮乏，但近年来随着代谢组学技术的广泛应用，不同菌种、菌株之间氨基酸代谢通路的差异得到深入阐明，新的氨基酸代谢中间产物和调控机制也相继被报道，这些

研究成果拓展了我们对细菌代谢网络的认识。在细菌致病性调控网络中，氨基酸代谢不仅广泛参与宿主环境适应和营养获取，还通过毒力因子产生、免疫逃逸、信号传导和抗生素耐药性等多重机制对细菌致病发挥关键作用。

尽管氨基酸代谢与病原细菌致病性存在显著关联，但其促进病原细菌致病进程的分子机制尚未完全阐明。深入揭示病原细菌氨基酸代谢网络与宿主细胞相互作用的分子机制不仅有助于阐明其致病进程，还可为开发新型抗菌药物和疫苗靶点提供理论依据和创新策略。本文系统综述了20种基本氨基酸(文中除特别指明为D-氨基酸外，均为L-氨基酸)以及D-氨基酸代谢途径与病原细菌致病机制之间的内在联系，着重阐述了天冬氨酸(aspartate, Asp)、支链氨基酸(branched-chain amino acids, BCAAs)等关键代谢节点的调控机制及其致病关联，以期为开发靶向氨基酸代谢的抗菌治疗策略提供新的视角。

## 1 病原细菌的氨基酸代谢

相较于人体依赖外源性供给必需氨基酸且分解代谢终产物相对固定的代谢模式，病原细菌的氨基酸代谢途径更为复杂多样。在合成代谢层面，多数病原细菌具备完整的氨基酸自主合成系统，能够通过多种途径高效合成自身所需的氨基酸<sup>[3]</sup>。例如，大肠杆菌(*Escherichia*

*coli*) 和谷氨酸棒杆菌 (*Corynebacterium glutamicum*) 可以通过莽草酸通路 (shikimate pathway) 合成芳香族氨基酸, 包括苯丙氨酸、酪氨酸和色氨酸等, 而人体因缺乏该通路需依赖外源性摄取<sup>[4]</sup>。在分解代谢层面, 病原细菌能够通过多种途径将氨基酸转化为能量或代谢中间体(如有机酸和醇)。例如, 某些梭菌属 (*Clostridium*) 可以通过 Stickland 发酵途径偶联氨基酸氧化还原获取 ATP<sup>[5]</sup>; 而一些沙门氏菌属 (*Salmonella*) 能够分解含硫氨基酸(如半胱氨酸和甲硫氨酸)生成硫化氢(hydrogen sulfide, H<sub>2</sub>S), 这是菌种鉴定和分型的重要表型<sup>[6]</sup>。此外, 病原细菌还能够代谢 D-氨基酸(如 D-丙氨酸和 D-谷氨酸), 这些 D-氨基酸在细菌细胞壁的肽聚糖合成中起重要作用<sup>[7]</sup>。

相对于宿主而言, 病原细菌具有独特的氨基酸代谢途径, 这对其生长繁殖及致病性具有重要意义, 也可能成为重要的药物靶点。通过筛选不同细菌氨基酸代谢途径中与其在宿主体内生存及致病相关的关键蛋白质或酶等, 可以为开发抗菌药物提供新思路。以半胱氨酸为例, 病原细菌依赖 O-乙酰丝氨酸硫醇裂解酶进行从头合成, 而哺乳动物缺失该通路。因此, 针对该途径中的关键酶开发抑制剂药物有望在治疗的同时减少药物对人体的副作用, 显著降低病原细菌的宿主毒性<sup>[8]</sup>。然而, 此类研究需要仔细评估药物对宿主细胞的影响, 以避免交叉反应对宿主造成潜在危害; 还需考虑体外环境和体内环境的差异: 在体外可以抑制病原细菌氨基酸代谢的药物, 在体内可能引发病原细菌掠夺宿主体内氨基酸的代偿反应, 使药物失去效果, 甚至对宿主造成更大的危害。为避免这种情况发生, 可以考虑同时将病原细菌中某种必需氨基酸的关键代谢酶及其转运酶作为靶点进行药物研发。

## 2 病原细菌的氨基酸代谢与其致病机制之间的关系

### 2.1 天冬氨酸

天冬氨酸是病原细菌生命活动关键的碳源和氮源。多数病原细菌体外生长主要通过草酰乙酸前体的转化或其他氨基酸的转氨作用进行内源合成; 而在宿主体内营养受限的环境中则需依赖外源摄取<sup>[9]</sup>。肠沙门氏菌 (*Salmonella enterica*) 通过二羧酸转运系统 (dicarboxylate uptake ATP binding cassette, DcuABC) 介导天冬氨酸和苹果酸的摄取, 激活厌氧条件下的 H<sub>2</sub>/延胡索酸呼吸链, 从而建立其小鼠肠道中的初始定殖优势<sup>[10]</sup>。研究证实, 感染早期宿主肠道内饮食来源的天冬氨酸通过维持延胡索酸呼吸为肠沙门氏菌的增殖提供了能量基础<sup>[11]</sup>。天冬氨酸在天冬氨酸裂解酶 (aspartate ammonia-lyase, AspA) 催化下分解生成延胡索酸和氨<sup>[12]</sup>, 前者可作为电子受体经琥珀酸途径驱动厌氧呼吸产能, 而后者则可通过 H<sup>+</sup> 中和参与肠沙门氏菌的酸耐受调控。值得注意的是, 在结肠炎进程中肠腔天冬氨酸水平呈现非饮食依赖性升高; 肠沙门氏菌可通过诱发小鼠肠道炎症促使巨噬细胞释放活性氧 (reactive oxygen species, ROS), 介导肠道菌群裂解释放天冬氨酸, 进而增强天冬氨酸依赖的厌氧延胡索酸呼吸, 最终促进肠沙门氏菌在肠道中的定殖及扩散<sup>[13]</sup> (图 1)。

天冬氨酸依赖的厌氧延胡索酸呼吸机制在致病性肠杆菌如大肠杆菌<sup>[11]</sup>和空肠弯曲杆菌 (*Campylobacter jejuni*)<sup>[14]</sup>中保守存在, 但不同菌属对宿主微环境的适应性存在显著差异。例如, 炎症肠道中天冬氨酸的升高使鼠伤寒沙门菌获得相对于共生大肠杆菌的生长优势<sup>[13]</sup>, 这可能源于其能够利用天冬氨酸衍生的延胡索酸和肠道硝酸盐作为电子受体协同进行厌氧呼吸。此外, 天冬氨酸代谢在其他病原细菌的宿主感染过程中同样发挥重要作用: 金黄色葡萄球菌 (*Staphylococcus aureus*) 骨感染模型中, 宿主感染

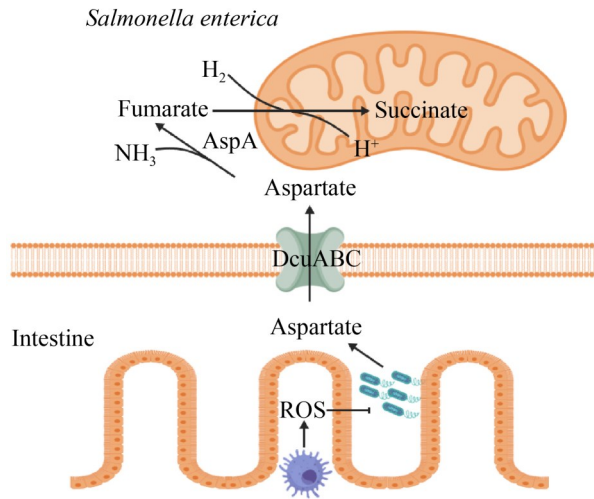


图1 肠沙门氏菌利用肠道菌群裂解释放的天冬氨酸进行厌氧延胡索酸呼吸

Figure 1 *Salmonella enterica* utilizes aspartate released by the lysis of the intestinal microbiota for anaerobic fumarate respiration. Created with BioGDP.com.

组织中富集的谷氨酸抑制了金黄色葡萄球菌对天冬氨酸的外源摄取,使其需要依赖天冬氨酸的内源性合成维持感染<sup>[15]</sup>;结核分枝杆菌(*Mycobacterium tuberculosis*)相关研究揭示,靶向抑制天冬氨酸代谢关键酶(如天冬氨酸氨基转移酶 Rv3722c)可显著降低其巨噬细胞毒性和小鼠毒力<sup>[16]</sup>。鼠疫耶尔森氏菌(*Yersinia pestis*)的天冬氨酸氨基裂解酶基因(*aspA*)突变后丧失活性,使其在多种胁迫环境中适应度下降,繁殖受到显著抑制<sup>[17]</sup>。现有研究虽已明确天冬氨酸代谢缺陷对病原细菌毒力的影响,但其内在机制及分子调控网络仍有待系统解析。值得关注的是,天冬氨酸作为氮源代谢的枢纽物质之一,是合成异亮氨酸、甲硫氨酸、赖氨酸、苏氨酸等多种氨基酸的前体物质。因此,其代谢扰动可能会间接影响这些下游氨基酸的代谢稳态。在研究过程中需充分考虑氨基酸互相转化的复杂性,聚焦解析在病原细菌致病过程中起最直接、最核心调控作用的氨基酸代谢通路。

## 2.2 支链氨基酸

支链氨基酸(BCAAs)包括亮氨酸、异亮氨酸和缬氨酸,BCAAs不仅是蛋白质生物合成的必需底物,也是革兰氏阳性细菌细胞膜支链脂肪酸生物合成的前体<sup>[18]</sup>。多效性转录因子蛋白Y (cellular oligopeptide and DNA-binding protein Y, CodY)是一种全局转录调控因子,几乎存在于所有低G+C含量革兰氏阳性菌中,如金黄色葡萄球菌和粪肠球菌(*Enterococcus faecalis*)。在这些细菌中CodY广泛调控数百个基因的转录,其靶基因主要编码代谢相关蛋白,部分靶基因则直接或间接调控必需毒力因子的表达;因此,CodY被视为代谢和毒力之间的调控枢纽,在介导病原细菌共生状态和致病状态之间的转换中发挥关键作用<sup>[19]</sup>。BCAAs和GTP可作为营养状态的信号分子,通过调控CodY的活性影响病原细菌的代谢适应性和毒力基因表达网络<sup>[20]</sup>。值得注意的是,CodY主要发挥阻遏因子的功能,即通过特异性结合靶基因启动子区的CodY box序列来阻遏RNA聚合酶或转录激活因子的结合,或者通过路障机制提前终止转录<sup>[21]</sup>。因此,在营养丰富的环境中(高BCAAs/GTP水平)CodY处于活性状态,导致其调控基因的表达普遍受到抑制(图2)。

以金黄色葡萄球菌为例,CodY对金黄色葡萄球菌的毒力因子合成具有重要的调控作用,其缺失会导致多种毒力因子(如分泌性蛋白酶、白细胞毒素和溶血素等)表达失调,同时因蛋白酶过度降解胞外基质导致生物被膜形成能力显著降低<sup>[22]</sup>。值得注意的是,CodY可通过感应BCAAs水平直接调控金黄色葡萄球菌透明质酸酶(hyaluronidase, HysA)的表达,这一分泌性致病因子通过分解宿主透明质酸促进肺组织侵袭,HysA的缺失导致金黄色葡萄球菌在小鼠肺部感染模型中显著减毒<sup>[23]</sup>。因此,BCAAs的获取对于金黄色葡萄球菌的增殖、环境适应性及毒力至关重要。BCAAs作为CodY的激活剂,可通过2种模式实现其调控功能。(1)在环境中

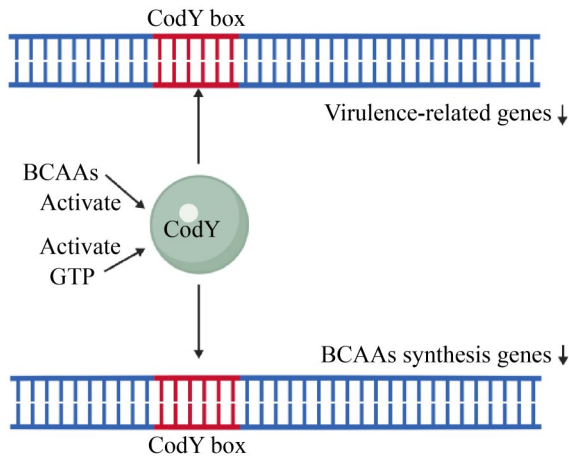


图2 BCAAs结合CodY抑制病原细菌BCAAs合成和毒力相关基因的表达

Figure 2 BCAAs in combination with CodY inhibit the expression of BCAAs synthesis and virulence-related genes in pathogenic bacteria. Created with BioGDP.com.

BCAAs充足时金黄色葡萄球菌通过Q型BCAAs转运蛋白 (branched-chain amino acid Q-type transporter, BrnQ) (如 BrnQ1、BrnQ2 等) 摄取外界 BCAAs, BCAAs 协同 GTP 增强 CodY 的抑制活性, 抑制靶标基因表达以避免冗余代谢, 从而高效利用宿主资源促进病原细菌的快速增殖<sup>[24]</sup>。(2) 在 BCAAs 限制条件下, 金黄色葡萄球菌通过 2 种机制激活 BCAAs 的合成通路, 一种是通过异亮氨酸依赖的 CodY 反式调控解除 CodY 对 BCAAs 合成基因的抑制作用, 即异亮氨酸缺乏使 CodY 抑制活性降低, 从而激活 BCAAs 合成基因的表达; 二是亮氨酸缺乏时通过亮氨酸响应的衰减子进行顺式调控, 阻止转录终止结构的形成, 从而促进 BCAAs 合成相关基因的表达<sup>[25]</sup>。

在金黄色葡萄球菌中发现的 BCAAs-CodY 轴致病调控功能具有跨物种保守性, 在病原细菌中广泛存在。在 BCAAs (尤其是异亮氨酸) 限制环境中单核增生李斯特氏菌 (*Listeria monocytogenes*) 的 CodY 活性下降, 导致正向调控因子 A (positive regulatory factor A, *prfA*)、李

斯特菌溶血素 O (listeriolysin O, *hly*) 和肌动蛋白聚集因子 A (actin assembly-inducing protein A, *actA*) 等关键毒力基因的表达上调<sup>[26]</sup>。炭疽芽孢杆菌 (*Bacillus anthracis*) 在缺乏外源 BCAAs 的环境下出现明显的生长缺陷, 且 BCAAs 转运蛋白 BrnQ3 或 BCAAs 合成相关基因二羧基酸脱水酶 (dihydroxy-acid dehydratase, *ilvD*) 的缺失均导致其对小鼠毒力明显减弱, 表明 BCAAs 的摄取和合成对于炭疽芽孢杆菌的毒力至关重要; 炭疽毒素激活因子 (anthrax toxin Activator, AtxA) 的活性受 BCAAs (特别是缬氨酸) 剂量依赖性激活<sup>[18]</sup>。此外, 弗朗西丝氏菌属 (*Francisella*) 某些亚种 (如减毒活疫苗株 LVS) 丧失 BCAAs 生物合成能力, 形成依靠异亮氨酸通透酶 (isoleucine permease, *IleP*) 的严格宿主异亮氨酸依赖性感染模式<sup>[27]</sup>。上述研究表明, BCAAs 不仅是病原细菌生长的重要营养物质, 更是连通环境信号与致病进程的关键枢纽, 其调控网络的深入解析将为靶向代谢干预的新型抗菌策略提供理论支撑。

BCAAs-CodY 轴调控的靶基因主要参与代谢途径过程, 涵盖多种氨基酸代谢通路。与野生型金黄色葡萄球菌相比,  $\Delta codY$  突变体中多种氨基酸 (包括 BCAAs 和天冬氨酸) 的水平显著升高<sup>[28]</sup>。上述现象提示氨基酸代谢调控网络具有广泛交联, 单一氨基酸浓度的扰动可能触发复杂的级联反应。因此, 在研究氨基酸代谢与致病机制的关联时, 必须充分考虑这种网络的整体性和交互性。

### 2.3 其他氨基酸

谷氨酰胺代谢在不同病原细菌致病过程中呈现多维度调控特征。结核分枝杆菌以谷氨酰胺为主要氮源维持其在人巨噬细胞中的存活与增殖<sup>[29]</sup>。单核增生李斯特氏菌以细胞内谷氨酰胺浓度阈值作为环境信号和诱导因子调控致病基因的表达<sup>[30]</sup>。幽门螺杆菌 (*Helicobacter pylori*)  $\gamma$ -谷氨酰转肽酶 ( $\gamma$ -glutamyltranspeptidase, *gGT*) 通过剥夺胃黏膜中的谷氨酰胺抑制 T 细胞功能并建立其免疫耐受微环境<sup>[31]</sup>。在肺炎链球菌

(*Streptococcus pneumoniae*)中谷氨酰胺合成酶(glutamine synthetase, GlnA)活性可促进其初始定殖, 而谷氨酸/谷氨酰胺转运蛋白(GlnP)则可通过抵抗巨噬细胞吞噬和杀伤作用促进肺炎链球菌的肺部生存和血液传播<sup>[32]</sup>。此外, B群链球菌(group B *Streptococci*)的谷氨酰胺转运蛋白(GlnQ)可能通过影响胞质谷氨酰胺水平调控纤连蛋白黏附素的表达, 进而促进其纤连蛋白黏附和侵袭<sup>[33]</sup>。值得注意的是, 鼠疫耶尔森氏菌的*glnALG*操纵子缺失突变体既丧失了谷氨酰胺合成能力, 也无法通过摄取或分解代谢维持细胞内谷氨酰胺稳态, 导致其毒力完全丧失; 该突变株免疫小鼠和豚鼠后可对野生株感染提供有效的保护性免疫, 为开发安全有效的减毒活疫苗提供了新靶点<sup>[34]</sup>。这一发现揭示了氨基酸代谢干预在疫苗设计中的巨大潜力, 提示针对其他依赖特定氨基酸的病原菌同时抑制其合成及摄取能力可以成为开发相应疫苗的新策略。

色氨酸代谢网络在病原细菌生存及感染策略中同样发挥关键作用。牙龈卟啉单胞菌(*Porphyromonas gingivalis*)通过色氨酸-吡啶通路刺激牙周炎生物被膜形成并诱导口腔微生物群失调<sup>[35]</sup>; 鳃利斯顿氏菌(*Listonella anguillarum*)中色氨酸合酶(tryptophan synthase, TrpA)的缺失导致其生物被膜形成减少、毒力减弱<sup>[36]</sup>。以上研究表明, 色氨酸代谢途径可能与病原细菌生物被膜的形成密切相关。此外, 结核分枝杆菌通过色氨酸生物合成保护自身免受CD4<sup>+</sup>T细胞介导的杀伤效应<sup>[37]</sup>。幽门螺杆菌则通过激活犬尿氨酸氨基转移酶II(kynurenine Aminotransferase II, KAT2)介导色氨酸代谢的犬尿氨酸途径, 促进胃肠上皮化生进程; 靶向抑制犬尿氨酸途径可能为预防幽门螺杆菌感染引起的炎症提供新策略<sup>[38]</sup>。

此外, 其他氨基酸的代谢在病原细菌黏附定殖、免疫逃逸和毒力等致病机制中也发挥重要作用。其中, 某些氨基酸可能因结构相似在病原细菌致病过程中发挥类似的作用。例如,

谷氨酸、精氨酸及丝氨酸等均可通过提高病原细菌的酸耐受能力促进其在胃肠道的定殖<sup>[39-42]</sup>; 丝氨酸和组氨酸均可通过提高病原细菌在巨噬细胞内的生存能力进而促进其免疫逃逸<sup>[29,43-44]</sup>。结核分枝杆菌利用丙氨酸脱氢酶Rv2780水解宿主细胞内的丙氨酸, 从而抑制宿主抗菌肽的表达, 促进其在宿主细胞内的生存; 丙氨酸和Rv2780抑制剂GWP-042均显示出对结核分枝杆菌感染的抑制效果, 为开发新的抗结核治疗策略提供了潜在的靶点<sup>[45]</sup>。上述研究揭示了特定氨基酸代谢网络在病原细菌致病中的独特调控机制, 这些发现为深入研究其致病机制及相关抗菌治疗靶点提供了重要理论依据和实验基础(表1)。

### 3 D-氨基酸代谢在病原细菌致病过程中的作用

细菌可产生多种D-氨基酸参与细菌生长、生物被膜形成与扩散以及肽聚糖代谢的调节等生理活动<sup>[63]</sup>。除直接参与细菌细胞壁肽聚糖合成的D-丙氨酸和D-谷氨酸外, 细菌培养物上清液中还可检测到非典型D-氨基酸(noncanonical D-amino acids, NCDAA), 即其他通常认为不用于构建细胞壁肽聚糖的D-氨基酸<sup>[64]</sup>。深入研究表明, 这些NCDAA在细菌生长繁殖过程中也能够被整合到细胞壁肽聚糖中, 有助于病原细菌适应环境变化、增强其对抗外界威胁的能力, 并在侵入定殖时抵抗宿主蛋白酶水解消化<sup>[65]</sup>。例如, 鲍氏不动杆菌(*Acinetobacter baumannii*)可将D-赖氨酸整合到肽聚糖中, 这种肽聚糖编辑可提高其竞争优势<sup>[66]</sup>。在某些情况下, NCDAA可作为有毒的细胞外效应物干扰周围菌群的生长, 促进病原细菌在竞争激烈的多菌群环境中生存。霍乱弧菌(*Vibrio cholerae*)可产生D-精氨酸, 显著抑制多种微生物亚群的存活, 有利于其在胃肠道的定殖扩散<sup>[67]</sup>。此外, D-氨基酸还被认为是一种广泛存在的生物被膜分解信号,

表1 氨基酸代谢对病原细菌致病机制的影响及其关键分子

Table 1 The influence of amino acid metabolism on the pathogenic mechanism of pathogenic bacteria and its key molecules

Amino acid	Pathogenic bacteria	Key molecules	The influence on the pathogenic mechanism	References
Cysteine	<i>Acinetobacter baumannii</i>	GigC	Improve adaptability and virulence	[46]
Phenylalanine	<i>Acinetobacter baumannii</i>	Phenylpyruvate	Promote immune escape	[47]
Alanine	<i>Mycobacterium tuberculosis</i>	Rv2780	Promote immune escape	[45]
	<i>Pseudomonas aeruginosa</i>	DadA, DadX	Enhance competitive advantage	[48]
Glycine	<i>Clostridioides difficile</i>	GrdAB	Enhance virulence	[49]
Glutamic acid	<i>Acinetobacter baumannii</i>	GdhA	Maintain antibiotic resistance	[43]
	<i>Neisseria meningitidis</i>	GltT	Affect the development of meningitis	[50]
	<i>Listeria monocytogenes</i>	GadD	Promote gastric colonization	[39]
Methionine	<i>Salmonella enterica</i>	MetJ	Enhance virulence	[51]
Arginine	<i>Listeria monocytogenes</i>	ArcA	Promote gastric colonization	[39]
	<i>Staphylococcus aureus</i>	AhrC, ArcA1	Maintain chronic infection	[52]
	<i>Escherichia coli</i>	AdiA	Promote intestinal colonization	[40]
Lysine	<i>Staphylococcus aureus</i>	LysA	Support bloodstream infection	[53]
Tyrosine	<i>Clostridioides difficile</i>	HpdBCA, CodY	Promote intestinal colonization	[54]
Proline	<i>Helicobacter pylori</i>	PutA	Promote colonization and movement	[55]
	<i>Clostridioides difficile</i>	PrdB	Affect colonization and toxin production	[56]
Serine	<i>Mycobacterium abscessus</i>	WhiB7	Maintain antibiotic resistance	[57]
	<i>Escherichia coli</i>	SdaA, SdaB	Promote intestinal colonization	[41]
	<i>Bacillus abortus</i>	SerB	Maintain virulence	[58]
Threonine	<i>Mycobacterium tuberculosis</i>	SerC	Promote immune escape	[29]
	<i>Staphylococcus aureus</i>	ThrC	Support bloodstream infection	[53]
Asparagine	<i>Salmonella enterica</i>	AnsB	Promote immune escape and colonization	[59]
	<i>Francisella</i>	AnsP	Promote intracellular replication and dissemination	[60]
	<i>Helicobacter pylori</i>	Asparaginase	Promote immune escape	[61]
Histidine	<i>Acinetobacter baumannii</i>	HisC	Promote immune escape	[43]
	<i>Mycobacterium tuberculosis</i>	IFN- $\gamma$	Promote reproduction	[62]

NCDAAs 的积累会抑制细菌生物被膜的形成并促进生物被膜分解；该机制可能有利于过度密集的细菌群体从生物被膜中释放出来，进一步扩散繁殖<sup>[68]</sup>。还有研究表明，结核分枝杆菌在缺氧条件下释放的 D-丝氨酸可抑制 CD8<sup>+</sup> T 细胞产生干扰素(interferon, IFN)- $\gamma$ ，从而促进其免疫逃逸<sup>[69]</sup>。

病原细菌 D-氨基酸代谢的这些特性不仅有利于其繁殖扩散及致病，也为抗菌治疗带来了新的思路。例如，D-组氨酸可对抗铜绿假单胞菌

(*Pseudomonas aeruginosa*)的生物被膜形成从而增强其对抗生素阿米卡星的敏感性<sup>[70]</sup>。此外，许多含有天然和合成 D-氨基酸的肽(如短杆菌肽、杆菌肽、放线菌素等)通过形成离子通道破坏细菌细胞膜，从而杀灭细菌，被用作细菌拮抗剂<sup>[71]</sup>。其中，部分 D-氨基酸取代已成为提高抗菌肽体内活性的有效技术，为口服抗菌肽药物的研发提供了理论基础<sup>[72]</sup>。

目前，病原细菌 D-氨基酸代谢与其致病过程的联系主要聚焦于细胞壁合成和生物被膜形

成等方面, 其更深层次的调控机制仍待揭示。值得注意的是, 宿主内源性 D-氨基酸(除 D-丝氨酸外)主要源自共生菌群, 并通过酶促降解与排泄机制维持极低的生理浓度(如血液中 D-氨基酸通常不足相应 L-异构体的 10%)<sup>[73]</sup>。这一独特的宿主代谢特征为靶向病原细菌 D-氨基酸代谢提供了有效干预策略: 针对特定关键 D-氨基酸(如病原菌生存或毒力所必需的), 通过抑制其细菌源性合成可有效切断其供应来源, 进而使病原细菌丧失致病性。该“合成阻断”策略有望发展新型靶向抗菌疗法。

## 4 总结与展望

在病原细菌-宿主互作过程中氨基酸代谢的动态平衡对致病进程至关重要。宿主通过“营养免疫”策略限制入侵病原细菌对氨基酸等营养物质的获取<sup>[74]</sup>。与之相对的是, 病原细菌进化出“营养毒力”策略, 即通过分泌效应蛋白劫持宿主代谢通路特异性提升限制性氨基酸(如半胱氨酸)的利用度, 从而突破宿主“营养免疫”屏障并驱动病原细菌的胞内增殖<sup>[75]</sup>。病原细菌与宿主之间争夺精氨酸、天冬酰胺和色氨酸等重要氨基酸的营养斗争构成了致病进程中代谢对抗的关键环节<sup>[76]</sup>。

宿主体内的共生菌群在外来病原细菌感染后的代谢竞争中呈现双向调控作用。一方面, 某些共生菌的特定代谢产物可作为营养物质促进病原细菌致病过程。例如, 肠球菌属 (*Enterococcus*) 通过消耗精氨酸并释放可发酵氨基酸(如亮氨酸和鸟氨酸等)重塑宿主肠道代谢微环境, 增强抗生素扰动后艰难拟梭菌 (*Clostridioides difficile*) 在肠道中的定殖能力及致病性<sup>[77]</sup>。鼠伤寒沙门菌通过诱发宿主肠道炎症反应产生活性氧(ROS), 促使肠道共生菌裂解释放天冬氨酸并加以利用, 进而促进其在肠道中的定殖及扩散<sup>[13]</sup>。另一方面, 共生菌通过与病原细菌竞争氨基酸等营养物质抑制病原细菌定

殖<sup>[78]</sup>。例如, 肠道菌群可通过营养竞争等作用预防沙门氏菌的侵袭和感染<sup>[79]</sup>; 而肠道菌群的代谢产物吲哚丙酸(indolepropionic acid, IPA)作为色氨酸类似物, 可通过负反馈的形式阻断结核分枝杆菌的色氨酸合成途径从而抑制其生长<sup>[80]</sup>。

近年来, 研究表明在病原细菌感染宿主进程中氨基酸代谢通过调控黏附、定殖、侵袭、毒力因子释放及免疫逃逸等关键环节参与构建病原细菌的感染适应体系。本文系统综述了 20 种基本氨基酸以及 D-氨基酸代谢对不同病原细菌致病进程的促进机制, 重点阐述了天冬氨酸介导的鼠伤寒沙门菌在小鼠结肠炎感染进程中的厌氧呼吸优势, 以及 CodY 通过感知 BCAAs 对金黄色葡萄球菌等病原细菌毒力的调控机制, 勾勒了病原细菌感染进程中氨基酸代谢的核心驱动作用。

当前相关研究仍面临氨基酸代谢网络互作复杂性的严峻挑战。尽管能够通过单一氨基酸营养限制及特定基因敲除等方法鉴定某种氨基酸代谢对病原细菌致病进程的促进作用, 但由于氨基酸及其代谢物之间可相互转化, 所观测到的表型可能源于中间代谢物对其他代谢通路或关键基因的调控, 而非目标氨基酸本身的直接效应。因此, 未来研究应聚焦阐明代谢物交叉调控网络, 继续深入解析氨基酸代谢促进病原细菌致病过程的复杂网络和精确节点, 这些机制的阐明将为基于靶向氨基酸代谢开发新的抗菌治疗策略提供理论依据。

## 作者贡献声明

李嘉敏: 执行调研、撰写文章、完成呈现; 宋凯: 项目管理、审阅; 宋亚军: 获取基金、提出概念、审阅。

## 作者利益冲突公开声明

作者声明不存在任何可能会影响本文所报告工作的已知经济利益或个人关系。

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