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微生物群和色氨酸参与支气管肺发育不良发病的研究进展

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摘　要

支气管肺发育不良(Bronchopulmonary Dysplasia, BPD)是一种见于早产儿的慢性肺部疾病，其发生发展与多因素相互作用相关，并常导致心血管、神经等多系统远期后遗症。近年来，随着“肠－肺轴”概念的提出及深入研究，肠道微生物群及其代谢产物在BPD发病中的作用日益受到关注。色氨酸作为必需氨基酸，其代谢产物在免疫调节、屏障保护等方面具有重要作用。本文综述了肠道微生物及色氨酸代谢在BPD中的作用，重点总结BPD中存在的肠道菌群失调与色氨酸代谢紊乱及其潜在意义，旨在为深入理解BPD的发病机制及相关防治策略提供新的视角。

关键词

色氨酸，支气管肺发育不良，肠－肺轴，微生物群

Research Progress on the Involvement of Microbiota and Tryptophan in the Pathogenesis of Bronchopulmonary Dysplasia

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Abstract

Bronchopulmonary Dysplasia (BPD) is a chronic lung disease observed in premature infants, whose development is associated with the interplay of multiple factors and often leads to long-term sequelae in multiple systems such as the cardiovascular and nervous systems. In recent years, with the proposal and in-depth research on the concept of the "gut-lung axis," the role of gut microbiota and their metabolites in the pathogenesis of BPD has garnered increasing attention. Tryptophan, as an essential amino acid, plays a significant role in immune regulation and barrier protection through its metabolites. This article reviews the role of gut microbiota and tryptophan metabolism in BPD, focusing on summarizing the dysbiosis of gut microbiota and disturbances in tryptophan metabolism in BPD and their potential implications, aiming to provide new perspectives for a deeper understanding of the pathogenesis of BPD and related prevention and treatment strategies.

Keywords

Tryptophan, Bronchopulmonary Dysplasia, Gut-Lung Axis, Microbiota

1. 引言

支气管肺发育不良(Bronchopulmonary Dysplasia, BPD)是极早产儿常见的慢性肺部疾病，尽管新生儿重症监护技术不断进步，极早产儿的死亡率有所下降，但 BPD 的发病率仍然居高不下，甚至呈上升趋势[1] [2]。BPD 患儿再入院风险显著增高，且遗留心血管、神经发育及生长受限等多系统后遗症[3]-[5]。目前认为，BPD 是胎盘功能障碍、高氧暴露、呼吸机相关肺损伤及感染等多种因素共同作用于未成熟肺组织的结果[6] [7]。近年来，肠道微生物群及其代谢产物通过“肠–肺轴”参与疾病进程的研究不断深入，为理解 BPD 的复杂机制开辟了新途径。色氨酸是一种必需芳香族氨基酸，其在体内的代谢主要包括肝脏主导的犬尿氨酸途径、肠嗜铬细胞主导的 5-羟色胺途径和肠道微生物群主导的吲哚途径[8]-[10]。这些途径产生了喹啉酸、烟酸、犬尿氨酸、吲哚及其衍生物、5-羟色胺等多种活性代谢物，广泛参与氧化应激、血管生成、调节免疫和细胞增殖凋亡等病理生理过程[11]。本文旨在总结肠道菌群与色胺酸代谢在 BPD 中的研究进展，重点探讨 BPD 中存在的菌群失调、色氨酸代谢紊乱及其潜在作用机制，以期为该疾病的机制研究和治疗探索提供参考。

2. 肠道菌群与肠–肺轴

肠道不仅是消化吸收器官，也是人体重要的免疫和内分泌器官，通过多种机制与全身各系统相互作用[12]，肠道菌群及其代谢产物与 BPD 的进展紧密相关，该过程主要通过“肠–肺轴”这一双向通路实现。尽管肠道和呼吸道拥有各自独特的微生物群，但二者可通过代谢性产物、细胞外囊泡以及免疫细胞的表观遗传修饰等进行双向通讯[13] [14]。共享的微生物菌落及其代谢产物对于免疫稳态至关重要[13]-[15]。

早产儿由于胃肠道和免疫系统发育不成熟，加之早期抗生素使用、肠内喂养延迟等因素，极易发生肠道菌群失调[16] [17]。主要表现为微生物多样性降低、有益菌(如双歧杆菌)定植减少以及潜在致病菌过度生长[18] [19]。一项针对 45 名极低出生体重儿的研究表明，其肠道菌群组成与纠正胎龄相关，且演变过程可能出现障碍，例如肠球菌属的过度增值[20]。另一项研究显示，入住新生儿重症监护病房的早产儿肠道中金黄色葡萄球菌丰度较高，而有益健康的双歧杆菌科定植延迟，后者的定值通常伴随着更高的短链脂肪酸浓度和更低的 pH 值[21]。

3. 色氨酸代谢途径及其与肠道菌群的关联

3.1. 犬尿氨酸途径

犬尿氨酸途径是色氨酸在人体内主要的代谢通路，约有 90%的色氨酸经此途径代谢。该途径的限速酶主要包括肝脏中的色氨酸-2,3-双加氧酶(TDO)以及广泛分布于肠道上皮细胞和免疫细胞中的吲哚胺 2,3-双加氧酶 1 (IDO1) [22]。色氨酸经此途径转换为 N-甲酰犬尿氨酸(NFK)，进而转化为犬尿氨酸(KYNA)、3-羟基犬尿氨酸(3-HK)、3-羟基蒽酸(3-HAA)、丙氨酸、喹啉酸(QA)等代谢产物[11]。该途径与肠道密切联系，并且通过肠－肺轴与影响肺部免疫与炎症。

犬尿氨酸途径受到肠道微生物群的调控。有研究表明，嗜粘蛋白阿克曼菌的丰度与 IDO1 活性呈显著负相关，可下调 IDO1 表达缓解炎症反应[23]。纽约杜博西氏菌通过促进结肠固有层单个核细胞中 IDO1 的表达来调节 Treg/Th 17 应答，从而缓解右旋糖酐硫酸酯钠诱导的小鼠溃疡性结肠炎[24]。脆弱拟杆菌通过激活 Toll 样受体 2 (TLR2)上调树突状细胞中的 IDO1，而罗伊氏乳杆菌则通过 IL-10 介导的信号转导与转录激活因子 3 (STAT3)信号通路抑制其表达[25]。此外，细菌来源的短链脂肪酸(如丁酸盐)通过抑制信号转导与转录激活因子 1 (STAT1)和组蛋白去乙酰酶(HDAC)活性双重机制下调 IDO1 表达[26]。

3.2. 5-羟色胺途径

5-羟色胺(5-HT)的合成场所主要位于肠道和中枢神经系统，超过 95%的 5-HT 由肠道粘膜层的肠嗜铬细胞合成[8]。在中枢神经系统中，色氨酸在限速酶色氨酸羟化酶 2 (TPH2)的催化下羟化为 5-羟色氨酸，随后经芳香族 L-氨基酸脱羧酶作用脱羧生成 5-HT，最终作为重要的单胺神经递质发挥广泛生理作用，而在外周组织，5-HT 的合成主要由色氨酸羟化酶 2 (TPH1)介导，该过程主要发生于肠道嗜铬细胞，合成的 5-HT 释放到固有层后通过 5-羟色胺再摄取转运蛋白(SERT)被上皮细胞摄取，随后扩散到血液后被血小板摄取并储存，并通过血液循环分布至外周靶器官，参与多种生理过程的调节[27]。

肠道菌群可以影响 5-HT 合成。Myung 等发现，口服植物乳杆菌的小鼠肠道 TPH1 上调，提示其可能增强 5-HT 合成，同时在人体实验中发现服用植物乳杆菌组血清 5-HT 水平升高[28]。相反，肠致病性大肠杆菌通过蛋白酪氨酸磷酸酶抑制 5-羟色胺再摄取转运蛋白活性，从而降低 5-HT 含量，这与传染性腹泻病相关[29]。

3.3. 吲哚途径代谢及其与肠道菌群

吲哚途径由肠道中多种表达特定酶的细菌所驱动，其核心步骤是色氨酸酶催化的色氨酸向吲哚的转化过程。在该途径中，包括大肠杆菌、梭状芽孢杆菌属和拟杆菌属在内的多种细菌能将色氨酸转化为吲哚；而另一些细菌如乳酸杆菌、双歧杆菌属等能进一步代谢色氨酸生成包括吲哚-3-乙酸(IAA)、吲哚-3-乙醛(3-IAld)、吲哚-3-乳酸(ILA)、吲哚-3-丙酸(IPA)、色胺等多种活性衍生物[30]。

研究显示，将富含色氨酸的肠道代谢菌群移植到抗生素预处理的小鼠体内后，可显著提升结肠内吲哚水平，且拟杆菌属和乳杆菌属丰度与吲哚水平正相关[31]。同时 Pan 等人的研究表明，补充发酵乳杆菌

可增加吲哚及其衍生物(如3-吲哚乙酸)的浓度，并通过降低Kelch样ECH关联蛋白1 (Keap1)表达、提高核因子E2相关因子2 (Nrf2)及其下游血红素加氧酶1 (HO-1)和醌氧化还原酶1 (NQO-1)的表达，调节Nrf2-Keap1信号通路，增强机体抗氧化和抗炎能力[32]。

3.4. 三个途径相互影响

色氨酸的三大代谢途径在功能上相互关联与制约。色氨酸是三条通路的共同底物，根据酶的活性和肠道环境，IDO1/TDO、TPH1、色氨酸酶共同竞争底物色氨酸。当肠道或全身发生炎症时，IDO1被大量激活，驱动大部分色氨酸进入犬尿氨酸途径[33]。犬尿氨酸途径与吲哚途径的多种代谢物(如KYNA、IPA等)均可作为芳香烃受体(AhR)的配体，通过激活AhR信号通路参与维持肠道上皮稳态、调节肠道微生物群以及调节免疫耐受[8] [34] [35]。值得注意的是，同一途径的代谢物可能具有相反的免疫调节功能，例如犬尿氨酸常具有抗炎作用，而喹啉酸则被认为具有促炎特性[36]。进一步研究显示，感染过程中肥大细胞释放5-HT能够促进宿主保护性的犬尿氨酸途径，同时抑制吲哚途径，从而协助病原体清除和维持免疫稳态[37]。

4. BPD中的肠道菌群及色氨酸代谢紊乱

大量证据支持肠道菌群与色氨酸及其衍生物在BPD发展中的作用。动物实验显示，生后14天的BPD模型小鼠肠道菌群发生显著改变，拟杆菌门的相对丰度下降，而变形菌门的相对丰度增加[38]。同样，针对30名极早产儿的粪便分析发现，BPD组在生后28天时支原体门丰度较高而芽孢杆菌门丰度较低；生后28天内，BPD组的肠杆菌与解脲支原体的相对丰度显著增加，这表明肠道微生物菌群构成和演变异常，可能增强全身和肺部炎症反应，阻碍肺部发育[39]。对早产儿气道抽吸物的研究也发现，BPD婴儿出生时细菌多样性降低，并且随着时间推移拟杆菌门和变形菌门的相对丰度下降以及厚壁菌门的相对丰度增加，这种变化可能反映了代谢能力的变化，并且可能影响BPD相关的炎症过程[40]。针对有BPD风险的早产儿支气管肺泡灌洗液的研究发现，婴儿上下呼吸道与肠道的细菌群落结构存在差异，且在BPD风险更高的婴儿中下呼吸道出现了独特的菌群失调性炎症过程[41]。

近年来，色氨酸代谢紊乱被证实与支气管肺发育不良的发病机制密切相关[42]-[44]。在高氧诱导的BPD新生大鼠模型中，观察到肺组织内色氨酸–犬尿氨酸代谢途径的关键代谢物3-HAA水平出现显著且持续性的降低[42]。临床研究也发现，在新生儿呼吸窘迫综合征患儿的下呼吸道分泌物中，色氨酸及其衍生物(如犬尿氨酸、3-HK、IAA、ILA、IPA、QA)的含量均有所降低[45]。此外，在甲型流感病毒感染的小鼠血清代谢组学分析中，观察到IPA等肠道菌群来源的色氨酸代谢物减少，进一步研究显示，补充IPA能够降低病毒载量，并缓解肺部及全身性炎症反应[46]。在COVID-19患者中同样观察到色氨酸、5-羟色胺、色胺、吲哚丙酸、吲哚醋酸等多种色氨酸代谢物水平降低，而犬尿氨酸及3-羟基犬尿氨酸则与病情严重程度呈强正相关[47]。这些证据共同提示色氨酸代谢失衡是BPD病理过程中的重要环节。

BPD中的菌群失调通过改变色氨酸代谢通路中的关键酶影响下游免疫活性代谢物。乳酸菌属和双歧杆菌属在BPD动物模型和早产儿中丰度降低，前者能够将色氨酸转化为吲哚-3-醛，后者能利用色氨酸合成酶等利用外源性吲哚和丝氨酸合成吲哚-3-乳酸[42] [48]。尽管阿克曼菌在BPD中的丰度变化有待研究，然而近期发现该菌能增加血清中吲哚-3-丙酸的水平，激活保护性信号通路[49]。因此，BPD相关菌群失调引起了色氨酸代谢产物的变化。

5. 色氨酸及其衍生物参与BPD发病的作用机制

色氨酸及其衍生物通过免疫调节、屏障保护、抗氧化应激、微生物群的生态调控等方面参与BPD的发病过程。

5.1. 免疫调节

色氨酸及其衍生物可通过多种途径调节机体免疫反应。吲哚衍生物(如吲哚、吲哚乙酸)通过 AhR 依赖方式促进 IL-22 产生，并调节 Th17 和 3 型固有淋巴细胞(ILC3)，减轻肺部炎症[50]。吲哚丙酸(IPA)通过激活 PPARβ/δ 信号通路，促使 $CD4^+$T 细胞的能量代谢由糖酵解转向线粒体呼吸；该代谢重编程过程进一步影响其分化方向，选择性地抑制了促炎性 Th1 和 Th17 细胞，同时不影响调节性 T 细胞(Treg)功能，从而缓解肠道炎症[51]。此外，IPA、IAID 等代谢物还可通过激活 AhR，增强巨噬细胞的吞噬能力，并下调肺组织中 IL-1β、IL-6 和 TNF-α 等炎症因子水平，减轻小鼠肺部炎症反应[42] [52]。犬尿氨酸和 3-HAA 可诱导 Th1 细胞和自然杀伤细胞的凋亡，并下调 CD8 受体的表达，从而削弱其细胞毒性活性[33]。3-HAA 还能抑制脂多糖(LPS)激活的 PI3K/AKT/mTOR 和 NFκB 信号通路，减少 IL-6、TNF-α 等炎症因子释放，促进巨噬细胞由促炎 M1 型向抗炎 M2 型极化，从而发挥抗炎作用[53]。

5.2. 屏障保护

IPA 能促进杯状细胞分泌黏蛋白(MUC2, MUC4)及其相关因子(TFF3, REMLβ)，从而增强黏液层的结构与功能。同时 IPA 还能上调紧密连接蛋白(claudin-1、occludin 和 ZO-1)的表达，提高肠上皮细胞跨膜电阻并降低细胞间通透性，增强上皮屏障的完整性[54]。3 型固有淋巴细胞(ILC3)通过产生 IL-22 等细胞因子，促进上皮细胞代谢和黏蛋白分泌，在维持屏障免疫中发挥核心作用。色氨酸、吲哚丙烯酸、吲哚丙酸能强化肠固有层免疫细胞的活性，激活 AhR/STAT3/IL-22 信号通路，促进 ILC3 细胞从肠道向肺部的活化和迁移，增强强化肺屏障功能[55]。

5.3. 其他机制

补充 3-HAA 可缓解高氧诱导的 BPD 大鼠肺组织损伤。其机制包括通过直接结合铁蛋白重链 1 (FTH1)，干扰其与核受体共激活因子 4 (NCOA4)的相互作用，进而下调髓过氧化物酶(MPO)和环氧化酶 2 (COX2)表达，减轻炎症反应；同时上调肺表面活性蛋白 C (SPC)和水通道蛋白 5 (AQP5)表达。此外 3-HAA 通过降低酰基辅酶 A 合成酶长链家族成员 4 (ACSL4)、转铁蛋白(TF)、NCAO4 和微管相关蛋白 1 轻链 3B-II (LC3B-II)的蛋白和 mRNA 表达，并上调谷胱甘肽过氧化物酶 4 (GPX4)表达，抑制高氧诱导的肺组织铁死亡[44]。IDO1 过表达可促进转录因子 ATOH1 和 GFI1 上调，进而推动肠道上皮向杯状细胞、潘氏细胞、肠内分泌细胞和簇细胞等分泌性细胞谱系分化，促进黏液层形成和粘液相关菌群(如嗜粘蛋白阿克曼菌和谢氏黏液螺杆菌)的富集，增强溶菌酶分泌，从而提高对肠病原性大肠埃希杆菌的清除能力[56]。

6. 局限性

然而利用小鼠模型研究 BPD 发病机制从而转化到临床仍面临显著挑战。一方面小鼠模型大多基于炎症诱导，而人类 BPD 的产生是多因素的，与机械通气、高浓度氧气暴露、感染等多重因素相关[57]，小鼠模型难以复刻人类 BPD 复杂的病理生理过程。同时小鼠与人类在肠道菌群定植和免疫系统发育的时间窗具有种属差异，使得在特定时间上观察到小鼠模型的菌群色氨酸代谢难以直接对应到早产儿相对漫长的肠道菌群发育中[58]。其次，在新生儿重症监护室中，抗生素的使用对于肠道中具有色氨酸代谢能力的菌群同样具有杀伤作用，导致关键代谢物水平下降[59] [60]。

7. 总结

总而言之，肠道微生物群和色氨酸及其代谢物在 BPD 的发生发展具有重要作用。BPD 患儿常伴有肠道和肺部菌群紊乱与色氨酸代谢异常。这些变化可能通过影响免疫平衡、上皮屏障及氧化应激等多途径

参与疾病进展。这些发现进一步深化了对 BPD 肠肺轴的理解，有望为 BPD 的预防与治疗提供新的干预策略。

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