

肠道普氏菌属影响哮喘发生发展的机制研究进展

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摘 要

哮喘(Asthma)是儿童时期常见的慢性呼吸系统疾病。近几十年来,我国儿童哮喘的患病率总体呈上升趋势,造成极大的疾病危害与经济负担,对哮喘病因、发病机制的研究有益于哮喘的预防与治疗。微生物在人体健康与疾病中的作用研究日益增多,普雷沃氏菌属(以下简称普氏菌属)是人类肠道核心菌属之一。现有研究关于普氏菌属影响哮喘发生发展的机制尚不完全清楚,普氏菌属可能通过免疫调节、代谢调控等机制在哮喘病理生理过程中发挥作用。本综述旨在探讨肠道普氏菌属影响哮喘发生发展过程的作用机制,可增加读者对肠道普氏菌属与哮喘关联性的认识,为寻找研究新方向提供依据。

关键词

普雷沃氏菌属, 哮喘, 肠-肺轴, 免疫调节, 代谢调控

Research Progress on the Mechanism of Intestinal *Prevotella* Affecting the Occurrence and Development of Asthma

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Abstract

In recent decades, asthma has been a common chronic respiratory disease in children. The prevalence of asthma in children in China has generally been on the rise, causing great disease harm and economic burden. Research on the causes and pathogenesis of asthma is beneficial to the prevention and treatment of asthma. There is an increasing number of studies on the role of microorganisms in human health and disease. *Prevotella* is one of the core bacterial genera in the human intestine. Existing studies have not yet fully clarified the mechanism by which *Prevotella* affects the occurrence and development of asthma. *Prevotella* may play a role in the pathophysiological process of asthma through mechanisms such as immunomodulation and metabolic regulation. This review aims to explore the mechanism of intestinal *Prevotella* influencing the occurrence and development of asthma, which can increase readers' understanding of the association between intestinal *Prevotella* and asthma and provide a basis for finding new research directions.

Keywords

Prevotella, Asthma, Gut-Lung Axis, Immunomodulation, Metabolic Regulation

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1. 引言

哮喘为儿童期常见的慢性呼吸系统疾病, 是一种以气道高反应性及慢性气道炎症为主要特征的异质性疾病[1]。全球哮喘网络(GAN) I 期横断面研究显示, 青少年和儿童中哮喘的患病率约为 10%, 其中近一半有严重症状[2], 哮喘患病率在中低收入国家呈逐年上升趋势[1]。对哮喘病因、发病机制的研究有益于哮喘的预防和症状控制, 有助于减轻哮喘的疾病负担。

过敏、遗传易感性、病毒感染、空气污染等因素是哮喘发生发展的危险因素[3][4]。然而, 哮喘的确切病因尚不清楚。近年随着微生态研究的进展, 人们逐渐认识到微生物群与机体健康息息相关, 生命最初 100 天真菌和细菌微生物群对特异性喘息发展具有重要性[5]。人体微生物在胃肠道中密度最高, 被称为“肠道微生物组”[6], 已有较多证据表明, 人体肠道微生物群的组成与功能对哮喘的发病机制[7]、表型[8]、严重程度[9]有潜在影响。肠道中的主要菌门是拟杆菌门和厚壁菌门, 其次是放线菌门和变形菌门[10]。普氏菌属属于拟杆菌门, 作为肠道微生物群核心菌属之一, 其在哮喘发生发展中的作用存在相互矛盾的报道, 且作用机制尚不完全清楚。此综述旨在总结近年来肠道普氏菌属在儿童哮喘发生发展中作用机制的研究进展, 为探索其在哮喘的发病机制、进一步开发哮喘的微生态防治策略提供参考。

2. 普氏菌属的特点及分布

普氏菌属属于拟杆菌门、拟杆菌类、拟杆菌目、普雷沃氏菌科, 是一类革兰阴性、多形性无芽孢杆菌, 为专性厌氧菌, 对营养及生长环境要求较高[11], 故难以分离或培养。目前, 普雷沃氏菌属有 50 多种, 主要寄生于人和动物的口腔、肠道、阴道, 不含已知的专性致病菌种, 但其成员与人类多种疾病相关, 如牙周炎、软组织感染等机会性感染[12][13], 类风湿性关节炎、溃疡性结肠炎等肠道疾病[14][15], 肥胖、非酒精脂肪性肝病及糖尿病等代谢性疾病[16]-[18], 哮喘等呼吸道疾病[19]。

普氏菌属是肠道微生物群核心菌属之一, 其在健康人肠道中主要由 *Prevotella copri*、*Prevotella stercorea* 和相关谱系组成[20]。普氏菌属丰度受到饮食、抗生素使用、其他细菌等环境因素以及年龄的影响。多项研究(包括人群[21]-[23]及动物[24] [25]研究)显示, 高纤维饮食可以增加普氏菌丰度。因此, 普氏菌属在高纤维饮食人群的肠道中占主导, 被称为 2 型肠型[26]。De Filippis 等人报道了高纤维饮食可增加人肠道中普氏菌属丰度, 同时可增加粪便中 SCFAs 含量[23]。这是由于普氏菌属纤维降解酶的高表达, 短链脂肪酸(Short-Chain Fatty Acids, SCFAs)作为纤维降解酶降解复合碳水化合物和/或膳食纤维的副产品释放出来[24] [27]。而在使用氨苄西林(AMP)、万古霉素(VAN)后, 小鼠粪便中普氏菌属消失[28], 表明抗生素使用会引起普氏菌属丰度变化。最新研究指出, 在成年以前, 人肠道中普氏菌含量随年龄增长逐渐增加[29]。De Filippis 等人还报道了肠道微生物组中菌株水平的普氏菌多样性受饮食影响[30], 因此, 在验证宿主-微生物关联性时, 应该考虑饮食因素造成的菌株多样性差异对研究结果造成的影响。

3. 肠-肺轴

肺和肠道之间的联系已经在人类和动物研究中反复证明, 这种联系被称为“肠-肺轴”, 微生物群是这两个部位之间交互作用的重要因素[31]。两部位之间的交互作用是双向的: 肠道微生物群产生的代谢产物、内毒素和细胞因子进入连接肠道组织和肺的血流[32], 进而影响肺部免疫稳态[33], 而肺部刺激会导致肠道反应。例如, 幼稚免疫细胞最初在肠道中激活, 通过淋巴和血管游走至肺部发挥其效应功能[34]; 而用脂多糖(LPS)刺激小鼠肺会导致肠道中细菌数量显著增加[35], 提示肺炎可诱发肠道损伤[36]。

4. 肠道普氏菌属影响哮喘发生发展的作用机制

4.1. 免疫调节

4.1.1. 免疫反应

已经证实普氏菌属可影响宿主的免疫应答。T 细胞是免疫功能的重要组成部分, 初始 T 细胞活化后分化成功能不同的 T 细胞亚群, 分为辅助 T 细胞(Helper T Cell, Th)、调节性 T 细胞(Regulatory T Cell, Treg)和细胞毒性 T 细胞(Cytotoxic T Lymphocyte, CTL), 其中, 哮喘的病理生理过程较多涉及到 Th1、Th2、Th17、Treg 细胞, Th1/Th2 与 Th17/Treg 细胞免疫失衡是哮喘发生发展的重要免疫机制。Th2 主要分泌 Th2 型细胞因子, 包括 IL-4、IL-5、IL-6、IL-13 等, 哮喘发病与 Th2 型细胞因子过度分泌有关。而 Th17 通过分泌 IL-17、IL-21 等多种细胞因子参与炎症。Arrieta 等人发现肠道普雷沃氏菌科家族可诱导 Th2 型免疫应答[5]。普氏菌属与 Th17 型粘膜炎症增强有关, 可以激活 Th17 型免疫反应(肠道内 Th17 相关基因的表达水平[28]、Th17 细胞数量及血清中 Th17 相关细胞因子水平[37]均升高)和中性粒细胞募集, 阻碍 Treg 细胞产生[38], 从而破坏 Th17/Treg 免疫平衡。肠道普氏菌属通过激活 Th2、Th17 分泌促炎细胞因子介导哮喘的慢性炎症反应。一项研究发现口腔来源的 3 种普氏菌物种在哮喘患儿肠道中富集, 来自普氏菌的微生物模拟肽刺激炎症因子 IL-4、IL-5、IL-6、IL-8、IL-17A 产生, 而对照组肠道中未检测到普氏菌, 这说明口腔来源的普氏菌诱导的炎症可能通过微生物模拟肽刺激免疫反应, 从而参与儿童哮喘[39]。

然而, 也有报道称普氏菌属[40]及其代谢产物如丁酸盐等 SCFAs 可以促进白介素(IL)-10 的产生。众所周知, IL-10 是一种重要的抗炎或免疫抑制细胞因子。IL-10 的总体作用是下调促炎细胞因子如 IL-4 和 IL-5 [41]产生和促炎基因表达, 进而降低哮喘气道炎症反应[42]。日本研究者用 3 种哮喘相关细菌刺激嗜酸性粒细胞, 也观测到普氏菌属可能通过诱导 IL-10 产生参与抑制哮喘嗜酸性粒细胞炎症[40]。

4.1.2. 免疫耐受

脂多糖(LPS)是一种常见的病原体相关分子模式(Pathogen-Associated Molecular Pattern, PAMP), 是革兰阴性菌细胞壁中的特有成分。脂多糖(LPS)的生物合成与普氏菌呈正相关[17], 是普氏菌的重要毒力因

子[11], 主要与宿主细胞 TLR4 结合, 激活先天免疫系统细胞, 引发炎症反应。但普氏菌属对 TLR4 的刺激能力有限, 可能表现为低级别炎症反应进而驱动自身清除[43], 或在稳态条件下参与建立免疫耐受, 防止病原体入侵和慢性疾病的发生[44], 而不是致病性炎症反应。既往有研究证实少量的 LPS 可诱导内毒素免疫耐受[45] [46]。动物研究也有相同的发现: 使用低剂量 LPS 干预后, 哮喘小鼠气道高反应性显著降低[47]; 阿尔兹海默病小鼠肠道中普氏菌衍生的低剂量 LPS 通过诱导炎症耐受产生对结直肠癌肿瘤发生的耐药作用[48]。以上证据均佐证了低剂量 LPS 具有引发低度炎症、诱导免疫耐受的作用, 并且有助于改善哮喘的肺部炎症。因此, 普氏菌属可能通过产生 LPS 参与建立肺部免疫耐受, 从而抑制哮喘的病理生理过程。

4.2. 代谢调控

肠道微生物对哮喘的影响部分由细菌代谢产物介导。SCFAs 是目前已知的具有气道炎症保护特性的有益细菌代谢物之一, 主要包括乙酸、丙酸、丁酸。而本文中所述普氏菌属, 其成员擅长从植物多糖中提取 SCFAs [27] [49], 普氏菌属或通过产生 SCFAs 间接影响哮喘发生发展。农场环境研究(PASTURE)出生队列中, 学龄期儿童哮喘发病率与粪便中丁酸盐水平呈负相关[50]。SCFAs 可明显减轻屋尘螨诱导的中性粒细胞性哮喘小鼠肺部炎症, 包括减弱炎症细胞因子和炎症小体核苷酸结合寡聚化结构域样受体蛋白(NOD-Like Receptor Family Pyrin Domain Containing Protein, NLRP)-3 依赖性的气道重塑[51]。

SCFAs 具有增强肠上皮完整性的能力。微生物群结构及组成、代谢物的变化导致病原体相关分子模式(PAMPs)的泄漏[52], PAMPs 通过与宿主细胞上的模式识别受体(PPRs)结合(如 Toll 样受体、NOD 样受体), 激活免疫反应和炎症反应, 可引发全身低度炎症[52]。前文所述的“肠-肺轴”的概念表明, 肠道微生物群确实会引发肺部的炎症性疾病(如哮喘)[33]。因此, 肠道上皮屏障保持完整性可限制全身性内毒素血症, 可减少或避免“肠漏”引发的全身低度炎症。SCFAs 通过多种机制增强上皮完整性。SCFAs 直接识别结合免疫细胞上的 G 蛋白耦联受体(GPCR), 如 GPR41、GPR43, 激活 GPCR 信号传导通路, 促进上皮屏障[53]和免疫稳态[54]。丁酸盐是组蛋白去乙酰化酶(HDAC)非选择性抑制剂[55]-[57]。HDAC 与基因沉默、转录抑制有关, 具体来说, HDACs 的活性能够改变染色质的构象, 使其更加紧密, 从而减少转录因子与 DNA 的结合, 抑制基因的表达[58]。丁酸盐通过 HDAC 抑制促进基因转录, 有益于上皮完整性的维持[59]。过氧化物酶体增殖物激活受体(Peroxisome Proliferator-Activated Receptors, PPAR γ)是一个配体激活转录因子家族[60], 在大肠、免疫细胞上高表达[61] [62], 可被丁酸盐激活, 而不能被乙酸盐、丙酸盐激活[63]。该受体激活后可促进细菌 β -氧化过程和增加氧气消耗, 以维持肠道厌氧环境, 促进上皮屏障的完整性。但有效的 PPAR γ 激活可能仅限于一定浓度的丁酸盐暴露[54]。因此, SCFAs 的种类和浓度也是其发挥增强上皮完整性作用的影响因素。增加膳食纤维摄入和产生特定 SCFA 的细菌数量有益于增强上皮完整性。此外, 炎症小体和 IL-18 的产生对于维持肠上皮完整性至关重要。SCFAs 与 GPR109A、GPR43 的结合可激活炎症小体。

此外, SCFAs 影响宿主的粘膜免疫和全身免疫功能。哮喘本身是粘膜反应受损相关的疾病, 是以气道粘膜大量炎症细胞浸润为特征的慢性炎症性疾病。GPCR 家族(如 GPR41、GPR43)在免疫细胞(尤其是炎症细胞, 如嗜酸性粒细胞、肥大细胞、单核/巨噬细胞)上广泛表达, 可识别并结合 SCFAs, 从而影响粘膜免疫, 促进免疫稳态。SCFAs 通过多种途径影响 T 细胞的发育和分化: 一是刺激 CD4 + Foxp3 调节细胞, 减少产生促炎细胞因子, 影响 T 细胞趋向分化; 二是通过转化生长因子(TGF)- β 1 作用于肠上皮粘膜细胞进而促进自然调节性 T (nTreg)细胞的分化[20]; 三是激活 GPR41、GPR43 信号传导通路, 从而抑制 HDAC 活性以调节 T 细胞发育。SCFAs 还可通过削弱对树突状细胞的招募, 从而抑制 Th2 细胞功能[64]。

5. 总结与展望

哮喘发病机制复杂, 肠道微生物的确影响哮喘发生发展过程。但就肠道普氏菌属而言, 它对哮喘发生发展的影响及机制尚不完全清楚, 目前的研究显示其可能通过免疫调节或代谢调控发挥作用: 免疫调节包括通过调节免疫细胞数量及功能、细胞因子的分泌等影响免疫应答, 建立肺部免疫耐受; 代谢调控, 尤其是 SCFAs 通过多种机制增强肠上皮完整性、影响粘膜和全身免疫功能。而通过这些作用机制, 普氏菌属对哮喘宿主的病理生理学过程可能起到截然相反的影响。这些看似相反的影响可能由多种因素导致, 如普氏菌属的丰度和遗传多样性、细菌代谢产物的种类及浓度、细菌成分差异等, 尚需要进一步研究来明确普氏菌属, 尤其是物种和菌株水平的普氏菌在哮喘发生发展中的作用机制, 拓展哮喘防治新思路。

参考文献

- [1] Asher, M.I., Rutter, C.E., Bissell, K., Chiang, C., El Sony, A., Ellwood, E., *et al.* (2021) Worldwide Trends in the Burden of Asthma Symptoms in School-Aged Children: Global Asthma Network Phase I Cross-Sectional Study. *The Lancet*, **398**, 1569-1580. [https://doi.org/10.1016/s0140-6736\(21\)01450-1](https://doi.org/10.1016/s0140-6736(21)01450-1)
- [2] García-Marcos, L., Asher, M.I., Pearce, N., Ellwood, E., Bissell, K., Chiang, C., *et al.* (2022) The Burden of Asthma, Hay Fever and Eczema in Children in 25 Countries: GAN Phase I Study. *European Respiratory Journal*, **60**, Article 2102866. <https://doi.org/10.1183/13993003.02866-2021>
- [3] Busse, W.W., Lemanske, R.F. and Gern, J.E. (2010) Role of Viral Respiratory Infections in Asthma and Asthma Exacerbations. *The Lancet*, **376**, 826-834. [https://doi.org/10.1016/s0140-6736\(10\)61380-3](https://doi.org/10.1016/s0140-6736(10)61380-3)
- [4] Hauptman, M., Gaffin, J.M., Petty, C.R., Sheehan, W.J., Lai, P.S., Coull, B., *et al.* (2020) Proximity to Major Roadways and Asthma Symptoms in the School Inner-City Asthma Study. *Journal of Allergy and Clinical Immunology*, **145**, 119-126.E4. <https://doi.org/10.1016/j.jaci.2019.08.038>
- [5] Arrieta, M., Arévalo, A., Stiemsma, L., Dimitriu, P., Chico, M.E., Loor, S., *et al.* (2018) Associations between Infant Fungal and Bacterial Dysbiosis and Childhood Atopic Wheeze in a Nonindustrialized Setting. *Journal of Allergy and Clinical Immunology*, **142**, 424-434.E10. <https://doi.org/10.1016/j.jaci.2017.08.041>
- [6] Dwivedi, M., Powali, S., Rastogi, S., Singh, A. and Gupta, D.K. (2021) Microbial Community in Human Gut: A Therapeutic Prospect and Implication in Health and Diseases. *Letters in Applied Microbiology*, **73**, 553-568. <https://doi.org/10.1111/lam.13549>
- [7] Jin, Q., Ren, F., Dai, D., Sun, N., Qian, Y. and Song, P. (2023) The Causality between Intestinal Flora and Allergic Diseases: Insights from a Bi-Directional Two-Sample Mendelian Randomization Analysis. *Frontiers in Immunology*, **14**, Article 1121273. <https://doi.org/10.3389/fimmu.2023.1121273>
- [8] Zou, X., Wu, J., Ye, H., Feng, D., Meng, P., Yang, H., *et al.* (2021) Associations between Gut Microbiota and Asthma Endotypes: A Cross-Sectional Study in South China Based on Patients with Newly Diagnosed Asthma. *Journal of Asthma and Allergy*, **14**, 981-992. <https://doi.org/10.2147/jaa.s320088>
- [9] Wang, Z., Lai, Z., Zhang, X., Huang, P., Xie, J., Jiang, Q., *et al.* (2021) Altered Gut Microbiome Compositions Are Associated with the Severity of Asthma. *Journal of Thoracic Disease*, **13**, 4322-4338. <https://doi.org/10.21037/jtd-20-2189>
- [10] Rinninella, E., Raoul, P., Cintoni, M., Franceschi, F., Miggiano, G.A.D., Gasbarrini, A., *et al.* (2019) What Is the Healthy Gut Microbiota Composition? A Changing Ecosystem across Age, Environment, Diet, and Diseases. *Microorganisms*, **7**, Article 14. <https://doi.org/10.3390/microorganisms7010014>
- [11] Sharma, G., Garg, N., Hasan, S. and Shirodkar, S. (2022) *Prevotella*: An Insight into Its Characteristics and Associated Virulence Factors. *Microbial Pathogenesis*, **169**, Article 105673. <https://doi.org/10.1016/j.micpath.2022.105673>
- [12] Zheng, W., Peng, K.R., Li, F.B., Zhao, H., Jiang, L.Q., Chen, F.B. and Jiang, M.Z. (2021) Characteristics of Gastric Mucosa Microbiota in Children with Chronic Gastritis and Duodenal Ulcer. *Chinese Journal of Pediatrics*, **59**, 551-556.
- [13] Zhao-Fleming, H.H., Barake, S.R.S., Hand, A., Wilkinson, J.E., Sanford, N., Winn, R., *et al.* (2018) Traditional Culture Methods Fail to Detect Principle Pathogens in Necrotising Soft Tissue Infection: A Case Report. *Journal of Wound Care*, **27**, S24-S28. <https://doi.org/10.12968/jowc.2018.27.sup4.s24>
- [14] Scher, J.U., Sczesnak, A., Longman, R.S., Segata, N., Ubeda, C., Bielski, C., *et al.* (2013) Expansion of Intestinal *Prevotella copri* Correlates with Enhanced Susceptibility to Arthritis. *eLife*, **2**, e01202. <https://doi.org/10.7554/elife.01202>
- [15] Dillon, S.M., Lee, E.J., Kotter, C.V., Austin, G.L., Gianella, S., Siewe, B., *et al.* (2016) Gut Dendritic Cell Activation

- Links an Altered Colonic Microbiome to Mucosal and Systemic T-Cell Activation in Untreated HIV-1 Infection. *Mucosal Immunology*, **9**, 24-37. <https://doi.org/10.1038/mi.2015.33>
- [16] Moran-Ramos, S., Cerqueda-García, D., López-Contreras, B., Larrieta-Carrasco, E., Villamil-Ramírez, H., Molina-Cruz, S., *et al.* (2023) A Metagenomic Study Identifies a *Prevotella copri* Enriched Microbial Profile Associated with Non-alcoholic Steatohepatitis in Subjects with Obesity. *Journal of Gastroenterology and Hepatology*, **38**, 791-799. <https://doi.org/10.1111/jgh.16147>
 - [17] Yuan, H., Wu, X., Wang, X., Zhou, J. and Park, S. (2024) Microbial Dysbiosis Linked to Metabolic Dysfunction-Associated Fatty Liver Disease in Asians: *Prevotella copri* Promotes Lipopolysaccharide Biosynthesis and Network Instability in the *Prevotella* Enterotype. *International Journal of Molecular Sciences*, **25**, Article 2183. <https://doi.org/10.3390/ijms25042183>
 - [18] Mai, H., Yang, X., Xie, Y., Zhou, J., Wang, Q., Wei, Y., *et al.* (2024) The Role of Gut Microbiota in the Occurrence and Progression of Non-Alcoholic Fatty Liver Disease. *Frontiers in Microbiology*, **14**, Article 1257903. <https://doi.org/10.3389/fmicb.2023.1257903>
 - [19] Su, Y., Zhang, Y. and Xu, J. (2023) Genetic Association and Bidirectional Mendelian Randomization for Causality between Gut Microbiota and Six Lung Diseases. *Frontiers in Medicine*, **10**, Article 1279239. <https://doi.org/10.3389/fmed.2023.1279239>
 - [20] Yeoh, Y.K., Sun, Y., Ip, L.Y.T., Wang, L., Chan, F.K.L., Miao, Y., *et al.* (2022) *Prevotella* Species in the Human Gut Is Primarily Comprised of *Prevotella copri*, *Prevotella stercorea* and Related Lineages. *Scientific Reports*, **12**, Article No. 9055. <https://doi.org/10.1038/s41598-022-12721-4>
 - [21] Martínez, I., Stegen, J.C., Maldonado-Gómez, M.X., Eren, A.M., Siba, P.M., Greenhill, A.R., *et al.* (2015) The Gut Microbiota of Rural Papua New Guineans: Composition, Diversity Patterns, and Ecological Processes. *Cell Reports*, **11**, 527-538. <https://doi.org/10.1016/j.celrep.2015.03.049>
 - [22] Wu, G.D., Chen, J., Hoffmann, C., Bittinger, K., Chen, Y., Keilbaugh, S.A., *et al.* (2011) Linking Long-Term Dietary Patterns with Gut Microbial Enterotypes. *Science*, **334**, 105-108. <https://doi.org/10.1126/science.1208344>
 - [23] De Filippis, F., Pellegrini, N., Vannini, L., Jeffery, I.B., La Storia, A., Laghi, L., *et al.* (2015) High-Level Adherence to a Mediterranean Diet Beneficially Impacts the Gut Microbiota and Associated Metabolome. *Gut*, **65**, 1812-1821. <https://doi.org/10.1136/gutjnl-2015-309957>
 - [24] Rampelli, S., Schnorr, S.L., Consolandi, C., Turroni, S., Severgnini, M., Peano, C., *et al.* (2015) Metagenome Sequencing of the Hadza Hunter-Gatherer Gut Microbiota. *Current Biology*, **25**, 1682-1693. <https://doi.org/10.1016/j.cub.2015.04.055>
 - [25] Kovatcheva-Datchary, P., Nilsson, A., Akrami, R., Lee, Y.S., De Vadder, F., Arora, T., *et al.* (2015) Dietary Fiber-Induced Improvement in Glucose Metabolism Is Associated with Increased Abundance of *Prevotella*. *Cell Metabolism*, **22**, 971-982. <https://doi.org/10.1016/j.cmet.2015.10.001>
 - [26] Arumugam, M., Raes, J., Pelletier, E., Le Paslier, D., Yamada, T., Mende, D.R., *et al.* (2011) Enterotypes of the Human Gut Microbiome. *Nature*, **473**, 174-180. <https://doi.org/10.1038/nature09944>
 - [27] Chung, W.S.F., Walker, A.W., Bosscher, D., Garcia-Campayo, V., Wagner, J., Parkhill, J., *et al.* (2020) Relative Abundance of the *Prevotella* Genus within the Human Gut Microbiota of Elderly Volunteers Determines the Inter-Individual Responses to Dietary Supplementation with Wheat Bran Arabinoxylan-Oligosaccharides. *BMC Microbiology*, **20**, Article No. 283. <https://doi.org/10.1186/s12866-020-01968-4>
 - [28] Yoon, S., Lee, G., Yu, J., Lee, K., Lee, K., Si, J., *et al.* (2022) Distinct Changes in Microbiota-Mediated Intestinal Metabolites and Immune Responses Induced by Different Antibiotics. *Antibiotics*, **11**, Article 1762. <https://doi.org/10.3390/antibiotics11121762>
 - [29] Wu, J., Shen, H., Lv, Y., He, J., Xie, X., Xu, Z., *et al.* (2024) Age over Sex: Evaluating Gut Microbiota Differences in Healthy Chinese Populations. *Frontiers in Microbiology*, **15**, Article 1412991. <https://doi.org/10.3389/fmicb.2024.1412991>
 - [30] De Filippis, F., Pasolli, E., Tett, A., Tarallo, S., Naccarati, A., De Angelis, M., *et al.* (2019) Distinct Genetic and Functional Traits of Human Intestinal *Prevotella copri* Strains Are Associated with Different Habitual Diets. *Cell Host & Microbe*, **25**, 444-453.E3. <https://doi.org/10.1016/j.chom.2019.01.004>
 - [31] Marsland, B.J., Trompette, A. and Gollwitzer, E.S. (2015) The Gut-Lung Axis in Respiratory Disease. *Annals of the American Thoracic Society*, **12**, S150-S156. <https://doi.org/10.1513/annalsats.201503-133aw>
 - [32] Dang, A.T. and Marsland, B.J. (2019) Microbes, Metabolites, and the Gut-Lung Axis. *Mucosal Immunology*, **12**, 843-850. <https://doi.org/10.1038/s41385-019-0160-6>
 - [33] Walsh, C.J., Guinane, C.M., O'Toole, P.W. and Cotter, P.D. (2014) Beneficial Modulation of the Gut Microbiota. *FEBS Letters*, **588**, 4120-4130. <https://doi.org/10.1016/j.febslet.2014.03.035>
 - [34] Budden, K.F., Gellatly, S.L., Wood, D.L.A., Cooper, M.A., Morrison, M., Hugenholtz, P., *et al.* (2016) Emerging

- Pathogenic Links between Microbiota and the Gut-Lung Axis. *Nature Reviews Microbiology*, **15**, 55-63. <https://doi.org/10.1038/nrmicro.2016.142>
- [35] Sze, M.A., Tsuruta, M., Yang, S.J., Oh, Y., Man, S.F.P., Hogg, J.C., *et al.* (2014) Changes in the Bacterial Microbiota in Gut, Blood, and Lungs Following Acute LPS Instillation into Mice Lungs. *PLOS ONE*, **9**, e111228. <https://doi.org/10.1371/journal.pone.0111228>
- [36] Perrone, E.E., Jung, E., Breed, E., Dominguez, J.A., Liang, Z., Clark, A.T., *et al.* (2012) Mechanisms of Methicillin-Resistant Staphylococcus Aureus Pneumonia-Induced Intestinal Epithelial Apoptosis. *Shock*, **38**, 68-75. <https://doi.org/10.1097/shk.0b013e318259abdb>
- [37] Huang, Y., Tang, J., Cai, Z., Zhou, K., Chang, L., Bai, Y., *et al.* (2020) *Prevotella* Induces the Production of Th17 Cells in the Colon of Mice. *Journal of Immunology Research*, **2020**, Article ID: 9607328. <https://doi.org/10.1155/2020/9607328>
- [38] Larsen, J.M. (2017) The Immune Response to *Prevotella* Bacteria in Chronic Inflammatory Disease. *Immunology*, **151**, 363-374. <https://doi.org/10.1111/imm.12760>
- [39] Yan, T., Bao, Y., Cao, S., Jiang, P., Zhang, Z., Li, L., *et al.* (2024) The Investigation of the Role of Oral-Originated *Prevotella*-Induced Inflammation in Childhood Asthma. *Frontiers in Microbiology*, **15**, Article 1400079. <https://doi.org/10.3389/fmicb.2024.1400079>
- [40] Hosoki, K., Nakamura, A., Kainuma, K., Sugimoto, M., Nagao, M., Hiraguchi, Y., *et al.* (2013) Differential Activation of Eosinophils by Bacteria Associated with Asthma. *International Archives of Allergy and Immunology*, **161**, 16-22. <https://doi.org/10.1159/000350338>
- [41] Ouyang, W. and O'Garra, A. (2019) IL-10 Family Cytokines IL-10 and IL-22: From Basic Science to Clinical Translation. *Immunity*, **50**, 871-891. <https://doi.org/10.1016/j.immuni.2019.03.020>
- [42] Seehus, C.R., Kadavallore, A., Torre, B.d.l., Yeckes, A.R., Wang, Y., Tang, J., *et al.* (2017) Alternative Activation Generates IL-10 Producing Type 2 Innate Lymphoid Cells. *Nature Communications*, **8**, Article No. 1900. <https://doi.org/10.1038/s41467-017-02023-z>
- [43] Larsen, J.M., Musavian, H.S., Butt, T.M., Ingvorsen, C., Thysen, A.H. and Brix, S. (2015) Chronic Obstructive Pulmonary Disease and Asthma-Associated Proteobacteria, but Not Commensal *Prevotella* Spp., Promote Toll-Like Receptor 2-Independent Lung Inflammation and Pathology. *Immunology*, **144**, 333-342. <https://doi.org/10.1111/imm.12376>
- [44] Bassis, C.M., Erb-Downward, J.R., Dickson, R.P., Freeman, C.M., Schmidt, T.M., Young, V.B., *et al.* (2015) Analysis of the Upper Respiratory Tract Microbiotas as the Source of the Lung and Gastric Microbiotas in Healthy Individuals. *mBio*, **6**. <https://doi.org/10.1128/mbio.00037-15>
- [45] Yuan, G., Yu, Y., Ji, L., Jie, X., Yue, L., Kang, Y., *et al.* (2016) Down-Regulated Receptor Interacting Protein 140 Is Involved in Lipopolysaccharide-Preconditioning-Induced Inactivation of Kupffer Cells and Attenuation of Hepatic Ischemia Reperfusion Injury. *PLOS ONE*, **11**, e0164217. <https://doi.org/10.1371/journal.pone.0164217>
- [46] Bruse, N., Jansen, A., Gerretsen, J., Rijbroek, D., Wienholts, K., Arron, M., *et al.* (2023) The Gut Microbiota Composition Has No Predictive Value for the Endotoxin-Induced Immune Response or Development of Endotoxin Tolerance in Humans *in Vivo*. *Microbes and Infection*, **25**, Article 105174. <https://doi.org/10.1016/j.micinf.2023.105174>
- [47] 李斌恺, 赖克方, 沈璐, 等. BCG-LPS 对哮喘小鼠气道炎症和气道反应性的影响[J]. 岭南急诊医学杂志, 2016, 21(6): 553-555.
- [48] Zhang, N., Zhang, R., Jiang, L., Gao, Z., Xia, W., Ma, X., *et al.* (2024) Inhibition of Colorectal Cancer in Alzheimer's Disease Is Mediated by Gut Microbiota via Induction of Inflammatory Tolerance. *Proceedings of the National Academy of Sciences*, **121**, e2314337121. <https://doi.org/10.1073/pnas.2314337121>
- [49] Flint, H.J., Scott, K.P., Duncan, S.H., Louis, P. and Forano, E. (2012) Microbial Degradation of Complex Carbohydrates in the Gut. *Gut Microbes*, **3**, 289-306. <https://doi.org/10.4161/gmic.19897>
- [50] Stokholm, J., Blaser, M.J., Thorsen, J., Rasmussen, M.A., Waage, J., Vinding, R.K., *et al.* (2018) Maturation of the Gut Microbiome and Risk of Asthma in Childhood. *Nature Communications*, **9**, Article No. 141. <https://doi.org/10.1038/s41467-017-02573-2>
- [51] Tagé, B.S.S., Gonzatti, M.B., Vieira, R.P., Keller, A.C., Bortoluci, K.R. and Aimbire, F. (2024) Three Main SCFAs Mitigate Lung Inflammation and Tissue Remodeling Nlrp3-Dependent in Murine HDM-Induced Neutrophilic Asthma. *Inflammation*, **47**, 1386-1402. <https://doi.org/10.1007/s10753-024-01983-x>
- [52] Cani, P.D. (2018) Human Gut Microbiome: Hopes, Threats and Promises. *Gut*, **67**, 1716-1725. <https://doi.org/10.1136/gutjnl-2018-316723>
- [53] Macia, L., Tan, J., Vieira, A.T., Leach, K., Stanley, D., Luong, S., *et al.* (2015) Metabolite-Sensing Receptors GPR43 and GPR109A Facilitate Dietary Fibre-Induced Gut Homeostasis through Regulation of the Inflammasome. *Nature Communications*, **6**, Article No. 6734. <https://doi.org/10.1038/ncomms7734>
- [54] Yip, W., Hughes, M.R., Li, Y., Cait, A., Hirst, M., Mohn, W.W., *et al.* (2021) Butyrate Shapes Immune Cell Fate and

- Function in Allergic Asthma. *Frontiers in Immunology*, **12**, Article 628453. <https://doi.org/10.3389/fimmu.2021.628453>
- [55] Patricia, H., Ramona, R. and Wilfried, E. (2020) Histone Deacetylases as Targets in Autoimmune and Autoinflammatory Diseases. *Advances in Immunology*, **147**, 51-59.
- [56] Lawlor, L. and Yang, X.B. (2019) Harnessing the HDAC-Histone Deacetylase Enzymes, Inhibitors and How These Can Be Utilised in Tissue Engineering. *International Journal of Oral Science*, **11**, Article No. 20. <https://doi.org/10.1038/s41368-019-0053-2>
- [57] Hull, E.E., Montgomery, M.R. and Leyva, K.J. (2016) HDAC Inhibitors as Epigenetic Regulators of the Immune System: Impacts on Cancer Therapy and Inflammatory Diseases. *BioMed Research International*, **2016**, Article ID: 8797206. <https://doi.org/10.1155/2016/8797206>
- [58] Roper, S. and Esteller, M. (2007) The Role of Histone Deacetylases (HDACs) in Human Cancer. *Molecular Oncology*, **1**, 19-25. <https://doi.org/10.1016/j.molonc.2007.01.001>
- [59] Wang, R.X., Lee, J.S., Campbell, E.L. and Colgan, S.P. (2020) Microbiota-Derived Butyrate Dynamically Regulates Intestinal Homeostasis through Regulation of Actin-Associated Protein Synaptopodin. *Proceedings of the National Academy of Sciences*, **117**, 11648-11657. <https://doi.org/10.1073/pnas.1917597117>
- [60] Grygiel-Górniak, B. (2014) Peroxisome Proliferator-Activated Receptors and Their Ligands: Nutritional and Clinical Implications—A Review. *Nutrition Journal*, **13**, Article No. 17. <https://doi.org/10.1186/1475-2891-13-17>
- [61] Ghosh, S.K., Perrine, S.P., Williams, R.M. and Faller, D.V. (2012) Histone Deacetylase Inhibitors Are Potent Inducers of Gene Expression in Latent EBV and Sensitize Lymphoma Cells to Nucleoside Antiviral Agents. *Blood*, **119**, 1008-1017. <https://doi.org/10.1182/blood-2011-06-362434>
- [62] Marion-Letellier, R., Dechelotte, P., Iacucci, M. and Ghosh, S. (2008) Dietary Modulation of Peroxisome Proliferator-Activated Receptor Gamma. *Gut*, **58**, 586-593. <https://doi.org/10.1136/gut.2008.162859>
- [63] Byndloss, M.X., Olsan, E.E., Rivera-Chávez, F., Tiffany, C.R., Cevallos, S.A., Lokken, K.L., *et al.* (2017) Microbiota-Activated PPAR- γ Signaling Inhibits Dysbiotic Enterobacteriaceae Expansion. *Science*, **357**, 570-575. <https://doi.org/10.1126/science.aam9949>
- [64] 崔天怡, 刘佳蕊, 吕彬, 等. 肠道菌群及免疫调节与儿童哮喘关系的研究进展[J]. 中国全科医学, 2022, 25(8): 1021-1026.