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炎症性肠病发病机制的研究进展

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摘　要

炎症性肠病是一种以反复发作的慢性肠道炎症为特征的消化系统疾病，其发病机制复杂，尚未完全阐明。近年来，关于炎症性肠病的研究取得了诸多重要进展。本文将从遗传因素、免疫因素、肠道微生物因素和环境因素等角度出发，综述IBD发病机制的相关研究进展。

关键词

溃疡性结肠炎，发病机制，遗传因素，免疫因素，肠道微生物因素，环境因素

Progress in Study on Pathogenesis of Inflammatory Bowel Disease

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Abstract

Inflammatory bowel disease (IBD) is a digestive system disorder characterized by recurrent chronic intestinal inflammation, with a complex pathogenesis that remains not fully understood. In recent years, significant progress has been made in IBD research. This paper reviews the relevant research advances in the pathogenesis of IBD from the perspectives of genetic factors, environmental factors, immune factors, and gut microbiota.

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Keywords

Inflammatory Bowel Disease, Pathogenesis, Genetic Factors, Immune Factors, Gut Microbiota Factors, Environmental Factors

1. 背景

炎症性肠病(Inflammatory Bowel Disease, IBD)多年来一直是一个全球性的卫生保健问题，发病率持续上升[1] [2]。它以肠内慢性炎症和溃疡形成为特征，主要包括克罗恩病(Crohn's Disease, CD)和溃疡性结肠炎(Ulcerative Colitis, UC)。其因高患病率、低治愈率、疾病并发症和高昂医疗费用等特点，造成了其巨大的全球疾病负担[3]-[5]。已有多项研究调查了 IBD 对健康相关生活质量的影响、治疗成本和对患者及其家庭的个人影响，结果表明 IBD 的流行和发病率不仅影响国家经济，而且影响患者的心理和社会健康[4]-[7]。目前，IBD 的发病机制尚不明确，这也是导致其难治性的原因之一。但自 75~100 年前首次对其进行现代描述以来，一系列新研究正在逐渐揭示该疾病背后的主要病理和生理过程[8]。研究表明[9]-[12]，个体的遗传因素、环境因素、免疫因素、肠道微生物因素和其他因素各方面都参与了 IBD 的发生。本文总结归纳了其最新研究进展，以明确了解 IBD 的发病机制。

2. 遗传因素参与 IBD 的发生及进展

国内外多项关于 IBD 种族差异和遗传易感性的研究揭示，不同人群在 IBD 发病率、临床表现及疾病进展等方面存在显著差异。Molodecky 等[13]对近六十年 IBD 流行病学文献进行综合分析，发现北美洲、亚洲、欧洲的 UC 最高发病率分别为 19.2/10 万、6.3/10 万、24.3/10 万；CD 的最高发病率则分别为 20.2/10 万、5.0/10 万、12.7/10 万。结果表明西方国家的 IBD 发病率显著高于东方国家。另外，有研究[14]发现 IBD 的发病具有家族聚集性，CD 单卵双胞胎的发病率为 30%~58%，而 UC 为 10%~15%。IBD 患者一级亲属的发病风险较普通人群高 5 倍[15]。

随着分子生物学和基因组学技术的飞速发展，对遗传因素在 IBD 发病机制的理解已取得重大进展。Frank [16]和 Anderson [17]等通过全基因组关联荟萃分析，识别出了 47 个与 UC 相关和 71 个与 CD 相关的易感基因或位点，包括 IL-23 通路成员、NK2 相关的转录因子、SMAD3、ZMIZ1 等 28 个 UC 和 CD 共有的基因位点。2012 年 Jostins 等[18]在 IBD 遗传框架的研究中已鉴定了 163 个易感位点，其中有 110 个与 CD 和 UC 易感性都相关。2015 年，Liu 等[19]在前面的研究基础上新鉴别出 38 个易感性位点，使 IBD 易感性位点达到 200 余个。2017 年，哈佛大学[20]设计了一种新的精细化定位算法，运用到全世界 IBD 研究团队的约 60000 个样本的高密度基因型中，分析鉴定出了 94 个全基因组关联研究报道的 IBD 相关性位点，并将易感性位点锁定到单碱基变异的精度。目前，针对 IBD 的相关基因及其单核苷酸多态性的研究主要集中在以下几个方面：(1) 免疫相关基因：包括 Toll 样受体(Toll-like Receptors, TLRs)家族基因、淋巴细胞抗原 75 基因、IL-23 受体基因等[21] [22]；(2) 自噬相关基因：如 ATG16L1 基因、IRGM 基因、ULK1 等[23]；(3) 代谢相关基因：例如人胞外核苷三磷酸二磷酸水解酶 1 基因、细胞外基质蛋白 1 基因、线粒体相关基因等[24]。

3. 免疫因素参与 IBD 的发生及进展

免疫紊乱是包括 IBD 在内的许多慢性疾病最重要的病原特征之一[25]，被公认为是炎症性肠病发病机制中极为重要的因素之一[26]。目前，对于免疫因素参与 IBD 的发生主要从免疫细胞和细胞因子两个方面展开。

(1) T 细胞及其细胞因子

在炎症性肠病患者的肠道中，T 细胞的数量和功能均发生异常。特别是辅助性 T 细胞(Th 细胞)和调节性 T 细胞(Treg 细胞)之间的平衡被打破。Th 细胞可分化为 Th1、Th2 和 Th17 等亚型，分别产生不同的细胞因子，如干扰素-γ (IFN-γ)、白细胞介素-4 (IL-4)、白细胞介素-17 (IL-17)等。目前，Th17 被认为是 IBD 的主要致病因素[27]。IL-17 是一种连接获得性和先天性免疫系统的细胞因子，IL-17 由 Th17 细胞产生，并由转录因子维 A 酸受体相关孤立受体(ROR) γt 控制，IL-17 细胞因子家族包含 6 个成员，IL-17A，IL-17B，IL-17C，IL-17D，IL-17E 和 IL-17F [28]。IBD 患者肠黏膜中存在大量 Th17 细胞浸润，炎症组织中释放 IL-17 和 Th17 相关细胞因子的细胞数量也较正常组织增加[29]-[31]。Leppkes 等[32]发现 IL-17A 和 IL-17F 在 IBD 炎症发生发展过程中起到了正向作用，IL-17A 和 IL-17F 缺乏可显著降低炎症的严重程度。有临床试验证实 IL-8、IL-17 在 UC 患者的肠黏膜上皮中高表达且其表达水平与结肠炎的严重程度呈正相关[33]。Raza 等[34]研究证实，溃疡性结肠炎患者病情的严重程度与患者外周血单核细胞分泌的 IL-17 水平相关，但在克罗恩病患者身上没有得到体现，提示 Th17 在 2 种类型的炎症性肠病中起不同作用。此外，与健康人群相比，IBD 患者血清中的 IL-17 和 IL-23 水平显著升高，血清水平与疾病严重程度和持续时间相关，可以用作反映 IBD 活动性的生物标志物[35]-[38]。

(2) B 细胞及其细胞因子

B 细胞是骨髓来源的多能干细胞，机体发出的外源信号刺激 B 细胞后，可使其产生促炎细胞因子或抗炎细胞因子，参与免疫调节和炎症反应，因此 B 细胞在炎症性肠病的发病中也发挥重要作用。调节性 B 细胞(Regulatory B cells, Bregs)是 B 细胞的一种，包括一组异质的不同免疫抑制性 B 细胞亚群，其具有不同的表型和功能特性[39]。有研究[40]逐步证明了源自 Bregs 的白细胞介素-10 (IL-10)在抑制不同的自身免疫模型中的关键作用。据研究，来自溃疡性结肠炎 UC 患者的 $CD19^{+}CD25^{+}CD71^{+}CD73^{-}$Bregs 表现出了较低的 IL-10 分泌能力，而 $CD4^{+}CD25^{+}$T 细胞增殖增加却相对较高[41]。又有证据表明，肠系膜淋巴结中产生 IL-10 的 B 细胞通过直接下调与 IL-10 相关的炎症级联反应来调节 TCRα 被敲除的小鼠慢性结肠炎的进展[42]。由此可见，产生 IL-10 的 Bregs 也会参与 IBD 的发病机制。

(3) 单核吞噬细胞

单核吞噬细胞(巨噬细胞和树突状细胞)存在于肠道相关淋巴组织和肠道固有层，具有多种功能，包括吞噬抗原样本、清除致病物质、产生细胞因子和维持上皮屏障功能。近年来，有研究表明巨噬细胞和树突状细胞等都参与了 IBD 的发生[43]-[47]。肠道巨噬细胞释放细胞因子和其他可溶性因子有助于维持组织稳态，向受损的结肠上皮传递再生信号，促进肠道再生反应[48] [49]。根据巨噬细胞不同表型及其分泌的不同细胞因子，可分为 M1 型(经典激活)和 M2 型(替代激活)两种极化类型[50]-[52]。然而伴随着微环境的不断改变，巨噬细胞极化为 M1 型和 M2 型，这两种表型的巨噬细胞在调节炎症反应的过程中通常可以相互转换。一旦巨噬细胞极化失衡，其产生的促炎细胞因子和抗炎细胞因子则失去平衡，就会引发和加剧 IBD [52]。

此外，树突状细胞是迄今为止发现的抗原提呈能力最强的一类专职的抗原提呈细胞，它在启动免疫应答与诱导耐受过程中发挥关键作用[53]。树突状细胞的成熟状态影响其功能，成熟的树突状细胞可通过上调 MHC II 和共刺激分子 CD40，B7-1 和 B7-2 启动免疫应答，而不成熟或半成熟的树突状细胞诱导抗

原特异性免疫耐受从而改善 IBD 的炎症反应[45]。

4. 肠道微生物因素参与 IBD 的发生及进展

人体肠道微生物群是一个复杂的生态系统，肠道内细菌数量约为 1.0×10^{14}，超过 1000 种[54] [55]。连同真菌、病毒、古细菌类微生物等主要密集地分布于结肠部位，且以厚壁菌门、拟杆菌、放线菌和变形菌为主[56]。在稳态条件下，肠道微生物群与宿主细胞在肠道生态系统中保持互惠关系：宿主细胞为微生物提供栖息环境和营养，而肠道微生物群则支持人类肠道的解剖、生理和免疫系统的发育[57]。在健康成年人中，肠道微生物群的主要部分由革兰氏阳性菌(厚壁菌门和放线菌门)和革兰氏阴性菌(变形菌门和拟杆菌门)组成[58]。肠道微生物群的改变(如多样性、丰度、数量和组成的丧失)会导致免疫反应失调，从而引发慢性炎症[59] [60]。IBD 患者肠道内微生物群的种类及数量均与正常人群不同，表明肠道微生物群失调在 IBD 的发病机制中发挥着关键作用[61]-[63]。

另外，变形菌门被认为是微生物群失调的标志[58]。在健康成人中，厚壁菌门和拟杆菌门构成了肠道微生物群的 90%，而变形菌门则占少数[58]。硫酸还原弧菌、大肠杆菌、克雷伯氏菌和志贺氏菌是变形菌门在肠道微生物群中的主要代表[58]。在四大主要门类(厚壁菌门、拟杆菌门、变形菌门和放线菌门)中，变形菌门是最不稳定的。变形菌门的过度生长是肠道微生物群失调的微生物标志。IBD 患者的研究表明，厚壁菌门明显减少，而变形菌门增多[64]。导致 IBD 中变形菌门过度生长的确切机制尚未解释[65]。

在当前的研究中，变形菌门的相对增加被认为是 IBD 的一个特征性标志[66]。与健康对照组相比，IBD 患者(包括 UC 和 CD)中附着侵袭性大肠杆菌的数量增加[66]-[68]。作为革兰氏阴性菌的主要组成，变形菌门在肠道微生物生态系统中的丰度增加会增强粘膜免疫系统对脂多糖和鞭毛蛋白的暴露，导致免疫反应失调，包括上皮屏障的丧失、抗菌肽和促炎性细胞因子生成的增加，以及树突状细胞和巨噬细胞的过度激活[66]。

IBD 涉及的特定变形菌门物种包括粘附侵袭性大肠杆菌、幽门螺旋杆菌和弯曲菌[64]。与健康对照组相比，Walker 等[69]发现 IBD 患者黏膜微生物群落结构会出现厚壁菌门占比减少，而拟杆菌占比增加的临床表现，并且炎症黏膜和正常黏膜间微生物群落细菌总体数量差异有统计学意义，IBD 患者肠道内双歧杆菌数量明显少于正常人群，变形杆菌却较正常人群增多。Bull 等[70]的研究在 CD 患者回肠黏膜中还发现有机会致病菌 *M. paratuberculosis* 定植。Berg 等[71]的研究发现 IBD 患者艰难梭菌感染风险较正常人群增高，Kang 等[72]也发现这种病原体在 CD 患者肠道微生物群中明显增加。Kleessen 等[73]利用免疫荧光原位杂交技术，发现与对照组相比，在近 83%的 UC 患者结肠黏膜标本中存在细菌对结肠黏膜的侵袭现象。Macfarlane 等[74]研究发现 UC 患者直肠中双歧杆菌数量约为正常对照组的 1/30，且 UC 患者的双歧杆菌优势菌群与正常对照组亦有明显不同。Barnich 等[75]在 CD 患者回肠中分离出一种能黏附并侵入肠上皮细胞的菌株，发现该菌株在 CD 患者肠粘膜中表达显著高于正常对照组。Martinez 等[76]还发现缓解期 UC 患者粪便中的微生物群具有生物多样性和稳定性，且随着缓解期的延长而呈现进行性下降。此外，UC 中还检测到了增多的硫酸盐还原变形菌[64]。

另外有研究表明，肠上皮细胞间紧密连接蛋白作用于肠上皮形成紧密连接的肠粘膜屏障功能，调节肠道通透性，控制肠粘膜下层及以下的通路[77]。当肠上皮遭到破坏时，黏膜失去抑制炎症反应的能力，导致肠道炎症的发生。肠上皮屏障功能的恢复可抑制肠道炎症的发生[78]。

5. 环境因素参与 IBD 的发生及进展

工业化后发展中国家 IBD 新的流行趋势表明，城市化过程中的环境暴露，包括饮食西化、吸烟、抗生素使用增加和早期微生物暴露等可能通过影响肠道微生物群、促进遗传易感人群发生肠道炎症，导致

IBD [79]。

在饮食方面，已有多项研究探讨了不同饮食因素与 IBD、CD 和 UC 发生及进展之间的关系[80]-[85]，但目前缺乏全面和最新的概述。另外，在 2019 年一项关于环境风险因素与 IBD 关系综述中及了一些饮食因素[86]。这其中几种饮食模式在炎症标志物(如 C-反应蛋白)方面具有改善效果，包括素食饮食[87] [88]、半素食饮食[87]、地中海饮食[89]和高摄入量的三文鱼[90]。此外，研究发现将菜籽油换为橄榄油与 UC 患者 C-反应蛋白水平下降相关[87]。类似地，增加芒果的摄入量也与促炎细胞因子减少相关[87]。对于 UC 患者，增加三文鱼的摄入量或通过增加纤维替代精制碳水化合物并未导致 C-反应蛋白显著变化[87]。

此外，吸烟是 IBD 最为人熟知的风险因素之一[91]。吸烟如何影响肠道微生物群尚不明确，但多项研究表明吸烟与微生物群失调相关。吸烟状态也会影响肠道微生物群，停止吸烟的健康个体中，厚壁菌门和放线菌门数量增加，而拟杆菌门和变形菌门数量减少。另外，吸烟被认为是 CD 的风险因素[92]。曾吸烟和现在吸烟的人群观察到较高的风险，包括预后较差、对类固醇、免疫抑制剂的需求增加以及与 IBD 相关的手术[92]-[94]。遗传易感性与吸烟对 CD 的影响相关[95]。然而，吸烟与 UC 之间呈负相关，即当前吸烟者与不吸烟者相比，UC 的风险较低[96]。此外，当前吸烟者的 UC 严重程度也较低[97]，UC 患者戒烟后通常与病情复发相关[97]。印度学者对 CD 患者的回顾性分析显示，口服烟草或吸烟对医学或外科治疗没有影响[98]。另外，在亚太地区 CD 和 UC 流行病学研究中[99]，吸烟并不是 CD 的风险因素，但曾经吸烟与 UC 相关联。

6. 结论

综上所述，炎症性肠病(IBD)是一种由遗传、免疫、肠道微生物群和环境等多种因素相互作用引发的复杂疾病。IBD 的特点包括肠道的慢性炎症、免疫反应失调以及复发和缓解的反复过程。研究 IBD 的发病机制对于深入理解其病理生理过程具有重要意义，有助于揭示潜在的危险因素、免疫反应异常以及微生物群失调等关键机制。这不仅能为早期诊断提供新思路，还能推动新型治疗策略的开发，改善患者的预后和生活质量。

参考文献

[1] Rudbaek, J.J., Agrawal, M., Torres, J., Mehandru, S., Colombel, J. and Jess, T. (2023) Deciphering the Different Phases of Preclinical Inflammatory Bowel Disease. *Nature Reviews Gastroenterology & Hepatology*, **21**, 86-100. https://doi.org/10.1038/s41575-023-00854-4

[2] Alatab, S., Sepanlou, S.G., Ikuta, K., Vahedi, H., Bisignano, C., Safiri, S., *et al*. (2020) The Global, Regional, and National Burden of Inflammatory Bowel Disease in 195 Countries and Territories, 1990-2017: A Systematic Analysis for the Global Burden of Disease Study 2017. *The Lancet Gastroenterology & Hepatology*, **5**, 17-30. https://doi.org/10.1016/s2468-1253(19)30333-4

[3] Sahoo, D.K., Heilmann, R.M., Paital, B., Patel, A., Yadav, V.K., Wong, D., *et al*. (2023) Oxidative Stress, Hormones, and Effects of Natural Antioxidants on Intestinal Inflammation in Inflammatory Bowel Disease. *Frontiers in Endocrinology*, **14**, Article ID: 1217165. https://doi.org/10.3389/fendo.2023.1217165

[4] Wang, R., Li, Z., Liu, S. and Zhang, D. (2023) Global, Regional and National Burden of Inflammatory Bowel Disease in 204 Countries and Territories from 1990 to 2019: A Systematic Analysis Based on the Global Burden of Disease Study 2019. *BMJ Open*, **13**, e065186. https://doi.org/10.1136/bmjopen-2022-065186

[5] Pizarro, T.T., Stappenbeck, T.S., Rieder, F., Rosen, M.J., Colombel, J., Donowitz, M., *et al*. (2019) Challenges in IBD Research: Preclinical Human IBD Mechanisms. *Inflammatory Bowel Diseases*, **25**, S5-S12. https://doi.org/10.1093/ibd/izz075

[6] Diederen, K., Haverman, L., Grootenhuis, M.A., Benninga, M.A. and Kindermann, A. (2018) Parental Distress and Quality of Life in Pediatric Inflammatory Bowel Disease: Implications for the Outpatient Clinic. *Journal of Pediatric Gastroenterology and Nutrition*, **66**, 630-636. https://doi.org/10.1097/mpg.0000000000001756

[7] Dou, Z., Zheng, H., Shi, Y., Li, Y. and Jia, J. (2024) Analysis of Global Prevalence, DALY and Trends of Inflammatory Bowel Disease and Their Correlations with Sociodemographic Index: Data from 1990 to 2019. *Autoimmunity Reviews*,

23, Article ID: 103655. https://doi.org/10.1016/j.autrev.2024.103655

[8] Strober, W., Fuss, I. and Mannon, P. (2007) The Fundamental Basis of Inflammatory Bowel Disease. *Journal of Clinical Investigation*, **117**, 514-521. https://doi.org/10.1172/jci30587

[9] Dowdell, A.S. and Colgan, S.P. (2021) Metabolic Host-Microbiota Interactions in Autophagy and the Pathogenesis of Inflammatory Bowel Disease (IBD). *Pharmaceuticals*, **14**, Article No. 708. https://doi.org/10.3390/ph14080708

[10] Guzzo, G.L., Andrews, J.M. and Weyrich, L.S. (2022) The Neglected Gut Microbiome: Fungi, Protozoa, and Bacteriophages in Inflammatory Bowel Disease. *Inflammatory Bowel Diseases*, **28**, 1112-1122. https://doi.org/10.1093/ibd/izab343

[11] Khan, I., Ullah, N., Zha, L., Bai, Y., Khan, A., Zhao, T., *et al*. (2019) Alteration of Gut Microbiota in Inflammatory Bowel Disease (IBD): Cause or Consequence? IBD Treatment Targeting the Gut Microbiome. *Pathogens*, **8**, Article No. 126. https://doi.org/10.3390/pathogens8030126

[12] Raoul, P., Cintoni, M., Palombaro, M., Basso, L., Rinninella, E., Gasbarrini, A., *et al*. (2022) Food Additives, a Key Environmental Factor in the Development of IBD through Gut Dysbiosis. *Microorganisms*, **10**, Article No. 167. https://doi.org/10.3390/microorganisms10010167

[13] Molodecky, N.A., Soon, I.S., Rabi, D.M., Ghali, W.A., Ferris, M., Chernoff, G., *et al*. (2012) Increasing Incidence and Prevalence of the Inflammatory Bowel Diseases with Time, Based on Systematic Review. *Gastroenterology*, **142**, 46-54.e42. https://doi.org/10.1053/j.gastro.2011.10.001

[14] Cader, M.Z. and Kaser, A. (2013) Recent Advances in Inflammatory Bowel Disease: Mucosal Immune Cells in Intestinal Inflammation. *Gut*, **62**, 1653-1664. https://doi.org/10.1136/gutjnl-2012-303955

[15] Park, J.B., Yang, S., Byeon, J., Park, E., Moon, G., Myung, S.J., *et al*. (2006) Familial Occurrence of Inflammatory Bowel Disease in Korea. *Inflammatory Bowel Diseases*, **12**, 1146-1151. https://doi.org/10.1097/01.mib.0000235094.01608.59

[16] Franke, A., McGovern, D.P.B., Barrett, J.C., Wang, K., Radford-Smith, G.L., Ahmad, T., *et al*. (2010) Genome-Wide Meta-Analysis Increases to 71 the Number of Confirmed Crohn's Disease Susceptibility Loci. *Nature Genetics*, **42**, 1118-1125. https://doi.org/10.1038/ng.717

[17] Anderson, C.A., Boucher, G., Lees, C.W., Franke, A., D'Amato, M., Taylor, K.D., *et al*. (2011) Meta-Analysis Identifies 29 Additional Ulcerative Colitis Risk Loci, Increasing the Number of Confirmed Associations to 47. *Nature Genetics*, **43**, 246-252. https://doi.org/10.1038/ng.764

[18] Jostins, L., Ripke, S., Weersma, R.K., Duerr, R.H., McGovern, D.P., Hui, K.Y., *et al*. (2012) Host-Microbe Interactions Have Shaped the Genetic Architecture of Inflammatory Bowel Disease. *Nature*, **491**, 119-124. https://doi.org/10.1038/nature11582

[19] Liu, J.Z., van Sommeren, S., Huang, H., Ng, S.C., Alberts, R., Takahashi, A., *et al*. (2015) Association Analyses Identify 38 Susceptibility Loci for Inflammatory Bowel Disease and Highlight Shared Genetic Risk across Populations. *Nature Genetics*, **47**, 979-986. https://doi.org/10.1038/ng.3359

[20] Huang, H., Fang, M., Jostins, L., Umićević Mirkov, M., Boucher, G., Anderson, C.A., *et al*. (2017) Fine-Mapping Inflammatory Bowel Disease Loci to Single-Variant Resolution. *Nature*, **547**, 173-178. https://doi.org/10.1038/nature22969

[21] 陆忠凯, 陈志荣, 朱俊义, 等. IL-23R 基因多态性与炎症性肠病的相关性[J]. 世界华人消化杂志, 2011, 19(19): 2076-2080.

[22] 何小华, 陈建勇. 炎症性肠病发病的相关免疫机制[J]. 南昌大学学报(医学版), 2011, 51(10): 93-96.

[23] 黄胜男, 李芳芳, 金丹. 自噬在炎症性肠病中作用机制的研究进展[J]. 细胞与分子免疫学杂志, 2022, 38(6): 559-564.

[24] 周文鹏, 白爱平. 炎症性肠病常见基因多态性[J]. 胃肠病学, 2018, 23(3): 177-180.

[25] Narasimamurthy, R., Hatori, M., Nayak, S.K., Liu, F., Panda, S. and Verma, I.M. (2012) Circadian Clock Protein Cryptochrome Regulates the Expression of Proinflammatory Cytokines. *Proceedings of the National Academy of Sciences*, **109**, 12662-12667. https://doi.org/10.1073/pnas.1209965109

[26] 姜雨薇, 金丹. 炎症性肠病免疫学发病机制研究进展[J]. 延边大学医学学报, 2014(1): 3.

[27] Chang, Y., Zhai, L., Peng, J., Wu, H., Bian, Z. and Xiao, H. (2021) Phytochemicals as Regulators of Th17/Treg Balance in Inflammatory Bowel Diseases. *Biomedicine & Pharmacotherapy*, **141**, Article ID: 111931. https://doi.org/10.1016/j.biopha.2021.111931

[28] Omrane, I., Baroudi, O., Bougatef, K., Mezlini, A., Abidi, A., Medimegh, I., *et al*. (2014) Significant Association between IL23R and IL17F Polymorphisms and Clinical Features of Colorectal Cancer. *Immunology Letters*, **158**, 189-194. https://doi.org/10.1016/j.imlet.2014.01.002

[29] Xu, Y., Shen, J. and Ran, Z. (2019) Emerging Views of Mitophagy in Immunity and Autoimmune Diseases. *Autophagy*, **16**, 3-17. https://doi.org/10.1080/15548627.2019.1603547

[30] Vincent, G., Novak, E.A., Siow, V.S., Cunningham, K.E., Griffith, B.D., Comerford, T.E., *et al*. (2020) Nix-Mediated Mitophagy Modulates Mitochondrial Damage during Intestinal Inflammation. *Antioxidants & Redox Signaling*, **33**, 1-19. https://doi.org/10.1089/ars.2018.7702

[31] Lee, S.H., Kwon, J.E. and Cho, M. (2018) Immunological Pathogenesis of Inflammatory Bowel Disease. *Intestinal Research*, **16**, Article No. 26. https://doi.org/10.5217/ir.2018.16.1.26

[32] Leppkes, M., Becker, C., Ivanov, I.I., Hirth, S., Wirtz, S., Neufert, C., *et al*. (2009) Rorγ-Expressing Th17 Cells Induce Murine Chronic Intestinal Inflammation via Redundant Effects of IL-17A and Il-17f. *Gastroenterology*, **136**, 257-267. https://doi.org/10.1053/j.gastro.2008.10.018

[33] Pearl, D.S., Shah, K., Whittaker, M.A., Nitch-Smith, H., Brown, J.F., Shute, J.K., *et al*. (2013) Cytokine Mucosal Expression in Ulcerative Colitis, the Relationship between Cytokine Release and Disease Activity. *Journal of Crohn's and Colitis*, **7**, 481-489. https://doi.org/10.1016/j.crohns.2012.07.022

[34] Raza, A., Ahmed, K., Navaneethan, U., Nady, S., Shata, M. and Giannella, R. (2011) The Levels of IL-17 Secreted by Lipopolysaccharide-Stimulated Eripheral Blood Mononuclear Cells (PBMC) in Inflammatory Bowel Disease (IBD) Patients Significantly Correlated with Disease Severity in Ulcerative Colitis but Not in Crohn's Disease. *American Journal of Gastroenterology*, **106**, S486. https://doi.org/10.14309/00000434-201110002-01275

[35] Neurath, M.F. (2019) IL-23 in Inflammatory Bowel Diseases and Colon Cancer. *Cytokine & Growth Factor Reviews*, **45**, 1-8. https://doi.org/10.1016/j.cytogfr.2018.12.002

[36] Aschenbrenner, D., Quaranta, M., Banerjee, S., Ilott, N., Jansen, J., Steere, B., *et al*. (2020) Deconvolution of Monocyte Responses in Inflammatory Bowel Disease Reveals an IL-1 Cytokine Network That Regulates IL-23 in Genetic and Acquired IL-10 Resistance. *Gut*, **70**, 1023-1036. https://doi.org/10.1136/gutjnl-2020-321731

[37] Lee, J., Hall, J.A., Kroehling, L., Wu, L., Najar, T., Nguyen, H.H., *et al*. (2020) Serum Amyloid a Proteins Induce Pathogenic Th17 Cells and Promote Inflammatory Disease. *Cell*, **180**, 79-91.e16. https://doi.org/10.1016/j.cell.2019.11.026

[38] Lucaciu, L.A., Ilieș, M., Vesa, Ș.C., Seicean, R., Din, S., Iuga, C.A., *et al*. (2021) Serum Interleukin (IL)-23 and IL-17 Profile in Inflammatory Bowel Disease (IBD) Patients Could Differentiate between Severe and Non-Severe Disease. *Journal of Personalized Medicine*, **11**, Article No. 1130. https://doi.org/10.3390/jpm11111130

[39] Jansen, K., Cevhertas, L., Ma, S., Satitsuksanoa, P., Akdis, M. and van de Veen, W. (2021) Regulatory B Cells, a to Z. *Allergy*, **76**, 2699-2715. https://doi.org/10.1111/all.14763

[40] Xie, J., Shi, C., Huang, H., Yang, W., Jiang, Y., Ye, L., *et al*. (2021) Induction of the Il-10-Producing Regulatory B Cell Phenotype Following Trichinella Spiralis Infection. *Molecular Immunology*, **133**, 86-94. https://doi.org/10.1016/j.molimm.2021.02.012

[41] Noh, J., Lee, J.H., Noh, G., Bang, S.Y., Kim, H.S., Choi, W.S., *et al*. (2010) Characterisation of Allergen-Specific Responses of Il-10-Producing Regulatory B Cells (br1) in Cow Milk Allergy. *Cellular Immunology*, **264**, 143-149. https://doi.org/10.1016/j.cellimm.2010.05.013

[42] Mizoguchi, A., Mizoguchi, E., Takedatsu, H., Blumberg, R.S. and Bhan, A.K. (2002) Chronic Intestinal Inflammatory Condition Generates Il-10-Producing Regulatory B Cell Subset Characterized by Cd1d Upregulation. *Immunity*, **16**, 219-230. https://doi.org/10.1016/s1074-7613(02)00274-1

[43] 孙晓睿, 张津铭, 方智芸, 等. 巨噬细胞极化在炎症性肠病中作用的研究进展[J]. 重庆医学, 2024, 53(12): 1889-1895.

[44] 张梦婷, 项镜蓉, 朱濛昕, 等. 巨噬细胞极化在炎症性肠病中的研究进展[J]. 胃肠病学, 2024, 29(1): 51-56.

[45] 肖瑶, 金丹. 树突状细胞在炎症性肠病中的作用研究进展[J]. 延边大学医学学报, 2020, 43(2): 148-151.

[46] 郑翠芳, 黄瑛. 锌指蛋白 A20 对树突状细胞的免疫调控及其在炎症性肠病发病机制中的作用[J]. 临床儿科杂志, 2016, 34(6): 470-474.

[47] 毛靖伟, 唐海英, 王英德. 树突状细胞、调节性 T 细胞在炎症性肠病中的研究进展[J]. 胃肠病学和肝病学杂志, 2010, 19(8): 762-765.

[48] Cardoso-Silva, D., Delbue, D., Itzlinger, A., Moerkens, R., Withoff, S., Branchi, F., *et al*. (2019) Intestinal Barrier Function in Gluten-Related Disorders. *Nutrients*, **11**, Article No. 2325. https://doi.org/10.3390/nu11102325

[49] Li, Y., Wang, Y., Liu, Y., Wang, Y., Zuo, X., Li, Y., *et al*. (2014) The Possible Role of the Novel Cytokines IL-35 and IL-37 in Inflammatory Bowel Disease. *Mediators of Inflammation*, **2014**, Article ID: 136329. https://doi.org/10.1155/2014/136329

[50] Na, Y.R., Stakenborg, M., Seok, S.H. and Matteoli, G. (2019) Macrophages in Intestinal Inflammation and Resolution:

A Potential Therapeutic Target in IBD. *Nature Reviews Gastroenterology & Hepatology*, **16**, 531-543. https://doi.org/10.1038/s41575-019-0172-4

[51] Bain, C.C. and Schridde, A. (2018) Origin, Differentiation, and Function of Intestinal Macrophages. *Frontiers in Immunology*, **9**, Article No. 2733. https://doi.org/10.3389/fimmu.2018.02733

[52] Moreira Lopes, T.C., Mosser, D.M. and Gonçalves, R. (2020) Macrophage Polarization in Intestinal Inflammation and Gut Homeostasis. *Inflammation Research*, **69**, 1163-1172. https://doi.org/10.1007/s00011-020-01398-y

[53] Mann, E.R. (2014) Intestinal Antigen-Presenting Cells in Mucosal Immune Homeostasis: Crosstalk between Dendritic Cells, Macrophages and *β*-Cells. *World Journal of Gastroenterology*, **20**, Article No. 9653. https://doi.org/10.3748/wjg.v20.i29.9653

[54] Sender, R., Fuchs, S. and Milo, R. (2016) Revised Estimates for the Number of Human and Bacteria Cells in the Body. *PLOS Biology*, **14**, e1002533. https://doi.org/10.1371/journal.pbio.1002533

[55] Hillman, E.T., Lu, H., Yao, T. and Nakatsu, C.H. (2017) Microbial Ecology along the Gastrointestinal Tract. *Microbes and environments*, **32**, 300-313. https://doi.org/10.1264/jsme2.me17017

[56] Sebastián Domingo, J.J. and Sánchez Sánchez, C. (2017) From the Intestinal Flora to the Microbiome. *Revista Española de Enfermedades Digestivas*, **110**, 51-56. https://doi.org/10.17235/reed.2017.4947/2017

[57] Kumar, S. and Kumar, A. (2022) Microbial Pathogenesis in Inflammatory Bowel Diseases. *Microbial Pathogenesis*, **163**, Article ID: 105383. https://doi.org/10.1016/j.micpath.2021.105383

[58] 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

[59] Sokol, H., Pigneur, B., Watterlot, L., Lakhdari, O., Bermúdez-Humarán, L.G., Gratadoux, J., *et al*. (2008) *Faecalibacterium prausnitzii* Is an Anti-Inflammatory Commensal Bacterium Identified by Gut Microbiota Analysis of Crohn Disease Patients. *Proceedings of the National Academy of Sciences*, **105**, 16731-16736. https://doi.org/10.1073/pnas.0804812105

[60] Darfeuille-Michaud, A., Boudeau, J., Bulois, P., Neut, C., Glasser, A., Barnich, N., *et al*. (2004) High Prevalence of Adherent-Invasive Escherichia Coli Associated with Ileal Mucosa in Crohn's Disease. *Gastroenterology*, **127**, 412-421. https://doi.org/10.1053/j.gastro.2004.04.061

[61] Lee, M. and Chang, E.B. (2021) Inflammatory Bowel Diseases (IBD) and the Microbiome—Searching the Crime Scene for Clues. *Gastroenterology*, **160**, 524-537. https://doi.org/10.1053/j.gastro.2020.09.056

[62] Kudelka, M.R., Stowell, S.R., Cummings, R.D. and Neish, A.S. (2020) Intestinal Epithelial Glycosylation in Homeostasis and Gut Microbiota Interactions in IBD. *Nature Reviews Gastroenterology & Hepatology*, **17**, 597-617. https://doi.org/10.1038/s41575-020-0331-7

[63] Cahana, I. and Iraqi, F.A. (2020) Impact of Host Genetics on Gut Microbiome: Take-Home Lessons from Human and Mouse Studies. *Animal Models and Experimental Medicine*, **3**, 229-236. https://doi.org/10.1002/ame2.12134

[64] Vester-Andersen, M.K., Mirsepasi-Lauridsen, H.C., Prosberg, M.V., Mortensen, C.O., Träger, C., Skovsen, K., *et al*. (2019) Increased Abundance of Proteobacteria in Aggressive Crohn's Disease Seven Years after Diagnosis. *Scientific Reports*, **9**, Article No. 13473. https://doi.org/10.1038/s41598-019-49833-3

[65] Knights, D., Silverberg, M.S., Weersma, R.K., Gevers, D., Dijkstra, G., Huang, H., *et al*. (2014) Complex Host Genetics Influence the Microbiome in Inflammatory Bowel Disease. *Genome Medicine*, **6**, Article No. 107. https://doi.org/10.1186/s13073-014-0107-1

[66] Shin, N., Whon, T.W. and Bae, J. (2015) Proteobacteria: Microbial Signature of Dysbiosis in Gut Microbiota. *Trends in Biotechnology*, **33**, 496-503. https://doi.org/10.1016/j.tibtech.2015.06.011

[67] Mirsepasi-Lauridsen, H.C., Vallance, B.A., Krogfelt, K.A. and Petersen, A.M. (2019) *Escherichia coli* Pathobionts Associated with Inflammatory Bowel Disease. *Clinical Microbiology Reviews*, **32**, e00060-18. https://doi.org/10.1128/cmr.00060-18

[68] Martinez-Medina, M., Aldeguer, X., Lopez-Siles, M., González-Huix, F., López-Oliu, C., Dahbi, G., *et al*. (2009) Molecular Diversity of Escherichia Coli in the Human Gut: New Ecological Evidence Supporting the Role of Adherent-Invasive *E. coli* (AIEC) in Crohn's Disease. *Inflammatory Bowel Diseases*, **15**, 872-882. https://doi.org/10.1002/ibd.20860

[69] Walker, A.W., Sanderson, J.D., Churcher, C., Parkes, G.C., Hudspith, B.N., Rayment, N., *et al*. (2011) High-Throughput Clone Library Analysis of the Mucosa-Associated Microbiota Reveals Dysbiosis and Differences between Inflamed and Non-Inflamed Regions of the Intestine in Inflammatory Bowel Disease. *BMC Microbiology*, **11**, Article No. 7. https://doi.org/10.1186/1471-2180-11-7

[70] Bull, T.J., McMinn, E.J., Sidi-Boumedine, K., Skull, A., Durkin, D., Neild, P., *et al*. (2003) Detection and Verification of *Mycobacterium avium* Subsp. *paratuberculosis* in Fresh Ileocolonic Mucosal Biopsy Specimens from Individuals with and without Crohn's Disease. *Journal of Clinical Microbiology*, **41**, 2915-2923.

https://doi.org/10.1128/jcm.41.7.2915-2923.2003

[71] Berg, A., Qazi, T., Wasan, S., Calderwood, A., Villafuerte-Gálvez, J., Kelly, C., *et al*. (2012) Antibodies to Clostridium Difficile Toxins in Inflammatory Bowel Disease Patients. *American Journal of Gastroenterology*, **107**, S616. https://doi.org/10.14309/00000434-201210001-01534

[72] Kang, S., Denman, S.E., Morrison, M., Yu, Z., Dore, J., Leclerc, M., *et al*. (2010) Dysbiosis of Fecal Microbiota in Crohn's Disease Patients as Revealed by a Custom Phylogenetic Microarray. *Inflammatory Bowel Diseases*, **16**, 2034-2042. https://doi.org/10.1002/ibd.21319

[73] Kleessen, B., Kroesen, A.J., Buhr, H.J. and Blaut, M. (2002) Mucosal and Invading Bacteria in Patients with Inflammatory Bowel Disease Compared with Controls. *Scandinavian Journal of Gastroenterology*, **37**, 1034-1041. https://doi.org/10.1080/003655202320378220

[74] Macfarlane, S., Furrie, E., Cummings, J.H. and Macfarlane, G.T. (2004) Chemotaxonomic Analysis of Bacterial Populations Colonizing the Rectal Mucosa in Patients with Ulcerative Colitis. *Clinical Infectious Diseases*, **38**, 1690-1699. https://doi.org/10.1086/420823

[75] Barnich, N., Carvalho, F.A., Glasser, A., Darcha, C., Jantscheff, P., Allez, M., *et al*. (2007) CEACAM6 Acts as a Receptor for Adherent-Invasive *E. coli*, Supporting Ileal Mucosa Colonization in Crohn Disease. *Journal of Clinical Investigation*, **117**, 1566-1574. https://doi.org/10.1172/jci30504

[76] Martinez, C., Antolin, M., Santos, J., Torrejon, A., Casellas, F., Borruel, N., *et al*. (2008) Unstable Composition of the Fecal Microbiota in Ulcerative Colitis during Clinical Remission. *The American Journal of Gastroenterology*, **103**, 643-648. https://doi.org/10.1111/j.1572-0241.2007.01592.x

[77] Turner, J.R. (2024) Intestinal Mucosal Barrier Function in Health and Disease. *Nature Reviews Immunology*.

[78] Fasano, A. (2011) Zonulin and Its Regulation of Intestinal Barrier Function: The Biological Door to Inflammation, Autoimmunity, and Cancer. *Physiological Reviews*, **91**, 151-175. https://doi.org/10.1152/physrev.00003.2008

[79] Ng, S.C., Shi, H.Y., Hamidi, N., Underwood, F.E., Tang, W., Benchimol, E.I., *et al*. (2017) Worldwide Incidence and Prevalence of Inflammatory Bowel Disease in the 21st Century: A Systematic Review of Population-Based Studies. *The Lancet*, **390**, 2769-2778. https://doi.org/10.1016/s0140-6736(17)32448-0

[80] Ge, J., Han, T., Liu, J., Li, J., Zhang, X., Wang, Y., *et al*. (2020) Meat Intake and Risk of Inflammatory Bowel Disease: A Meta-analysis. *The Turkish Journal of Gastroenterology*, **26**, 492-497. https://doi.org/10.5152/tjg.2015.0106

[81] Jaber, M., Altamimi, M., Altamimi, A., Cavaliere, S. and De Filippis, F. (2022) Mediterranean Diet Diminishes the Effects of Crohn's Disease and Improves Its Parameters: A Systematic Review. *Nutrition and Health*. https://doi.org/10.1177/02601060221102281

[82] Khademi, Z., Milajerdi, A., Larijani, B. and Esmaillzadeh, A. (2021) Dietary Intake of Total Carbohydrates, Sugar and Sugar-Sweetened Beverages, and Risk of Inflammatory Bowel Disease: A Systematic Review and Meta-Analysis of Prospective Cohort Studies. *Frontiers in Nutrition*, **8**, Article ID: 707795. https://doi.org/10.3389/fnut.2021.707795

[83] Khorshidi, M., Djafarian, K., Aghayei, E., *et al*. (2019) A Posteriori Dietary Patterns and Risk of Inflammatory Bowel Disease: A Meta-Analysis of Observational Studies. *International Journal for Vitamin and Nutrition Research*, **90**, 376-384.

[84] Milajerdi, A., Ebrahimi-Daryani, N., Dieleman, L.A., Larijani, B. and Esmaillzadeh, A. (2021) Association of Dietary Fiber, Fruit, and Vegetable Consumption with Risk of Inflammatory Bowel Disease: A Systematic Review and Meta-analysis. *Advances in Nutrition*, **12**, 735-743. https://doi.org/10.1093/advances/nmaa145

[85] Narula, N., Chang, N.H., Mohammad, D., Wong, E.C.L., Ananthakrishnan, A.N., Chan, S.S.M., *et al*. (2023) Food Processing and Risk of Inflammatory Bowel Disease: A Systematic Review and Meta-Analysis. *Clinical Gastroenterology and Hepatology*, **21**, 2483-2495.e1. https://doi.org/10.1016/j.cgh.2023.01.012

[86] Piovani, D., Danese, S., Peyrin-Biroulet, L., Nikolopoulos, G.K., Lytras, T. and Bonovas, S. (2019) Environmental Risk Factors for Inflammatory Bowel Diseases: An Umbrella Review of Meta-Analyses. *Gastroenterology*, **157**, 647-659.e4. https://doi.org/10.1053/j.gastro.2019.04.016

[87] Barros, V.J.d.S., Severo, J.S., Mendes, P.H.M., da Silva, A.C.A., de Oliveira, K.B.V., Parente, J.M.L., *et al*. (2021) Effect of Dietary Interventions on Inflammatory Biomarkers of Inflammatory Bowel Diseases: A Systematic Review of Clinical Trials. *Nutrition*, **91**, Article ID: 111457. https://doi.org/10.1016/j.nut.2021.111457

[88] Comeche, J.M., Gutierrez-Hervás, A., Tuells, J., Altavilla, C. and Caballero, P. (2020) Predefined Diets in Patients with Inflammatory Bowel Disease: Systematic Review and Meta-Analysis. *Nutrients*, **13**, Article No. 52. https://doi.org/10.3390/nu13010052

[89] Tian, Z., Zhuang, X., Zhao, M., Zhuo, S., Li, X., Ma, R., *et al*. (2021) Index-Based Dietary Patterns and Inflammatory Bowel Disease: A Systematic Review of Observational Studies. *Advances in Nutrition*, **12**, 2288-2300. https://doi.org/10.1093/advances/nmab069

[90] Charlebois, A., Rosenfeld, G. and Bressler, B. (2015) The Impact of Dietary Interventions on the Symptoms of Inflammatory Bowel Disease: A Systematic Review. *Critical Reviews in Food Science and Nutrition*, **56**, 1370-1378. https://doi.org/10.1080/10408398.2012.760515

[91] Thomas, T., Chandan, J.S., Li, V.S.W., Lai, C.Y., Tang, W., Bhala, N., *et al*. (2019) Global Smoking Trends in Inflammatory Bowel Disease: A Systematic Review of Inception Cohorts. *PLOS ONE*, **14**, e0221961. https://doi.org/10.1371/journal.pone.0221961

[92] Cosnes, J., Carbonnel, F., Beaugerie, L., Le Quintrec, Y. and Gendre, J. (1996) Effects of Cigarette Smoking on the Long-Term Course of Crohn's Disease. *Gastroenterology*, **110**, 424-431. https://doi.org/10.1053/gast.1996.v110.pm8566589

[93] Cosnes, J., Beaugerie, L., Carbonnel, F. and Gendre, J. (2001) Smoking Cessation and the Course of Crohn's Disease: An Intervention Study. *Gastroenterology*, **120**, 1093-1099. https://doi.org/10.1053/gast.2001.23231

[94] Cosnes,, Carbonnel,, Carrat,, Beaugerie,, Cattan, and Gendre, (1999) Effects of Current and Former Cigarette Smoking on the Clinical Course of Crohn's Disease. *Alimentary Pharmacology & Therapeutics*, **13**, 1403-1411. https://doi.org/10.1046/j.1365-2036.1999.00630.x

[95] Kuenzig, E., Eksteen, B., Barkema, H.W., Seow, C., Silverberg, M., Fedorak, R., *et al*. (2015) Age at Diagnosis of Crohn's Disease May Explain Nod2-Smoking Interactions. *American Journal of Gastroenterology*, **110**, S837. https://doi.org/10.14309/00000434-201510001-01975

[96] Bastida, G. (2011) Ulcerative Colitis in Smokers, Non-Smokers and Ex-Smokers. *World Journal of Gastroenterology*, **17**, Article No. 2740. https://doi.org/10.3748/wjg.v17.i22.2740

[97] Mokbel, M., Carbonnel, F., Beaugerie, L., *et al*. (1998) Effect of Smoking on the Long-Term Course of Ulcerative Colitis. *Gastroenterologie Clinique et Biologique*, **22**, 858-862.

[98] Arora, U., Ananthakrishnan, A.N., Kedia, S., Bopanna, S., Mouli, P.V., Yadav, D.P., *et al*. (2017) Effect of Oral Tobacco Use and Smoking on Outcomes of Crohn's Disease in India. *Journal of Gastroenterology and Hepatology*, **33**, 134-140. https://doi.org/10.1111/jgh.13815

[99] Ng, S.C., Tang, W., Ching, J.Y., Wong, M., Chow, C.M., Hui, A.J., *et al*. (2013) Incidence and Phenotype of Inflammatory Bowel Disease Based on Results from the Asia-Pacific Crohn's and Colitis Epidemiology Study. *Gastroenterology*, **145**, 158-165.e2. https://doi.org/10.1053/j.gastro.2013.04.007