

克罗恩病发病机制的研究进展： 遗传、环境与免疫因素

陈昌洪*, 石杰文, 朱代华#

重庆医科大学附属第二医院胃肠肛肠外科, 重庆

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摘 要

克罗恩病(Crohn's Disease, CD)是一种慢性复发性肠道炎症性疾病, 其发病机制复杂, 涉及遗传、环境和免疫等多个因素的相互作用。近年来, 随着基因组学、表观遗传学、蛋白组学和代谢组学等组学技术的发展, CD发病机制的研究取得了显著进展。全基因组关联研究(GWAS)发现了多个与CD相关的易感基因, 如NOD2和IL23R等, 这些基因参与免疫反应、肠道屏障功能及微生物组调节等多个生物学过程。此外, 环境因素如饮食习惯、吸烟和生活方式等也在CD的发生和发展中起着关键作用。免疫系统的异常反应, 包括免疫细胞功能紊乱、炎症介质释放失控以及自身免疫机制的参与, 是CD发病的核心环节。文章就克罗恩病发病机制的研究现状做出系统性概述。

关键词

克罗恩病, 发病机制, 遗传因素, 环境因素, 免疫功能紊乱

Research Progress on the Pathogenesis of Crohn's Disease: Genetic, Environmental, and Immune Factors

Changhong Chen*, Jiewen Shi, Daihua Zhu#

Department of Gastroenterology and Anorectal Surgery, The Second Affiliated Hospital of Chongqing Medical University, Chongqing

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*第一作者。

#通讯作者。

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Abstract

Crohn's Disease (CD) is a chronic relapsing intestinal inflammatory disease with a complex pathogenesis involving the interaction of multiple factors such as genetics, environment, and immunity. In recent years, with the development of omics technologies such as genomics, epigenetics, proteomics, and metabolomics, significant progress has been made in the research on the pathogenesis of CD. Genome-wide association studies (GWAS) have identified multiple susceptibility genes associated with CD, such as NOD2 and IL23R. These genes are involved in multiple biological processes, including immune response, intestinal barrier function, and microbiome regulation. In addition, environmental factors such as diet, smoking, and lifestyle also play a crucial role in the occurrence and development of CD. The abnormal response of the immune system, including dysfunction of immune cells, uncontrolled release of inflammatory mediators, and the involvement of auto-immune mechanisms, is the core link in the pathogenesis of CD. This article provides a systematic overview of the current research status of the pathogenesis of Crohn's disease.

Keywords

Crohn's Disease, Pathogenesis, Genetic Factor, Environmental Factor, Immune Dysfunction

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1. 前言

克罗恩病(Crohn's Disease, CD)是炎症性肠病(IBD)的主要亚型之一,以消化道的慢性复发性炎症为主要特征。从病理学角度看,CD的炎症性病变主要发生在回肠末端和结肠近端,呈现不连续、斑片状、节段性及透壁性特征。回结肠镜检查结合组织学检查已被确立为诊断的金标准[1]。近年来,CD的流行病学研究显示其发病率呈上升趋势,并且发病年龄逐渐年轻化[2]。CD的症状包括腹痛、腹泻、体重减轻和疲劳等,显著降低了患者的生活质量,给患者及其家庭和社会带来了沉重负担[1]。因此,深入探究其发病原因对疾病的预防和临床治疗具有重要意义。

CD的病因复杂,发病机制尚未完全明确。近年来的研究表明,CD的发病机制涉及遗传易感性、环境因素与免疫功能障碍之间的复杂相互作用。遗传易感性是CD的重要风险因素,基因组全关联研究(GWAS)发现超过240个与CD相关的遗传风险位点,但这些位点仅解释了不到30%的发病风险[3][4]。这表明环境因素在CD的发生和发展中也起着关键作用,尤其是在“西方化”生活方式日益普及的背景下,CD的发生率在一些东部国家显著上升[5]。环境因素的影响包括饮食习惯、生活方式(如吸烟)和肠道微生物群的组成等。研究表明,饮食可以改变肠道微生物群,从而影响免疫反应和炎症反应[5]。例如,高蛋白饮食可能导致肠道微生物群的变化,而这些变化与CD的症状和病理过程密切相关[6]。此外,免疫系统的异常反应也是CD发病机制的重要组成部分,过度的免疫反应可能导致肠道组织的损伤和慢性炎症[7]。

综上所述,CD的发病机制是多因素交互作用的结果,深入探讨遗传、环境和免疫等多个因素及其相互作用,有助于我们更好地理解CD的发病机制,并为未来的预防或治疗策略提供新的思路。

2. CD 发病机制的研究现状

2.1. 遗传因素在 CD 中的作用

2.1.1. 基因易感性研究

研究表明, CD 的发病与多种基因的易感性密切相关。近年来, 通过全基因组关联研究(GWAS), 已经识别出多个与 CD 相关的易感基因, 包括 NOD2 和 IL23R 等基因的多态性[8] [9]。这些基因涉及免疫反应、肠道屏障功能及微生物组调节等多个生物学过程。例如, IL-23 信号通路的基因变异被认为与 CD 的发病密切相关, 这一发现为靶向治疗提供了新的思路, 乌司奴单抗(一种 IL-12/23 拮抗剂)已获批用于治疗中重度的 CD [10]。此外, 研究还发现某些基因多态性, 如 IL-6 基因的 rs1800795 多态性, 与 CD 的发生风险存在显著相关性[11]。不同种族人群中, IL-6 基因 rs1800795 多态性与 CD 发病风险关联存在差异, 这体现了基因与环境因素对 CD 发病的综合影响, 同时也强调了遗传易感性在 CD 中的重要性, 并为个体化治疗提供了潜在的生物标志物。

2.1.2. 相关基因的功能与机制

CD 的发病机制涉及多个关键基因的功能异常。这些基因不仅参与免疫反应, 还与肠道屏障的完整性密切相关。例如, NOD2 基因的变异被认为会导致对肠道微生物的识别和清除能力下降, 进而引发异常的炎症反应[12]。ATG16L1 和 IRGM 基因与自噬过程密切相关, 这些基因的变异可导致自噬功能紊乱, 从而引发肠道微生物失衡和持续炎症[13] [14]。此外, 其他与 CD 相关的基因还包括 TNF- α 、IL-10、CARD15 等, 它们分别参与炎症因子的产生、免疫抑制和天然免疫识别等过程[15] [16]。研究发现, 肠道微生物组的组成与 CD 的遗传易感性相关, 特定的微生物群落可能通过调节宿主免疫反应影响疾病的进展[17]。目前的研究表明, 基因与环境因素之间存在复杂的相互作用, 然而, 目前对于这些相互作用的具体分子机制, 以及不同基因-环境组合对 CD 发病的相对贡献, 仍有待进一步深入研究。深入理解这些基因的功能及其在 CD 中的作用机制, 对于开发新的治疗策略具有重要意义。

2.1.3. 家族聚集性与遗传模式

流行病学研究表明, CD 具有明显的家族聚集倾向。CD 患者的一级亲属患病风险显著高于普通人群, 同卵双生子的一致率高达 50%, 而异卵双生子仅为 10%左右, 这提示 CD 具有较强的遗传倾向[18] [19]。然而, 在一些研究中, CD 的发病呈现出复杂的遗传模式, 包括可能的多基因遗传与环境因素的相互作用。家族聚集性研究发现, 某些家族中 CD 的发病率显著高于其他家庭, 提示这些家庭可能携带特定的遗传变异或环境暴露因素。目前认为, CD 可能是多个易感基因与环境因素相互作用导致疾病的发生与进展[20]。同时, 表观遗传学机制如 DNA 甲基化、组蛋白修饰等也可能参与 CD 的发病过程[21]。通过对不同家族遗传模式的比较分析, 结合环境因素的调查, 有助于进一步明确基因-环境相互作用在 CD 发病中的具体模式。未来研究可以采用多组学技术, 全面分析家族成员的遗传信息、表观遗传特征以及肠道微生物群落组成, 构建基因-环境-微生物相互作用网络, 深入探究 CD 的发病机制, 从而为 CD 的遗传咨询和早期干预提供更精准的依据。

2.2. 环境因素对 CD 的影响

2.2.1. 饮食习惯与肠道微生物群

饮食习惯在 CD 的发病机制中扮演着重要角色, 尤其是其对肠道微生物群的影响。研究表明, 饮食的组成可以显著改变肠道微生物的多样性和组成, 从而影响肠道的免疫反应。例如, 富含纤维的饮食能够促进有益菌群的生长, 而高脂肪和高糖的饮食则可能导致微生物群失调, 进而引发炎症反应[22] [23]。高纤维饮食可通过产生短链脂肪酸(SCFAs)来维持肠道微生物群的稳态和肠道屏障功能[24]。此外, 一些

特定的食物成分如红肉等也可能影响CD的发病[25][26]。CD患者常常表现出肠道微生物的多样性下降,并且特定的微生物群落与疾病活动性相关联。克罗恩病排除饮食(CDED)旨在减少接触可能促炎的饮食成分,这些成分对肠道微生物群、免疫反应和肠道屏障的负面影响介导。CDED已成为EEN的有效替代品,具有累积证据,包括随机对照试验,支持用于儿童和成人的诱导缓解和可能的维持[27]。因此,调整饮食结构,如采用CDED,可能有助于预防和控制CD的发生与发展[28]。然而,不同研究对于饮食习惯影响肠道微生物群进而影响CD发病的具体机制和程度存在差异。未来需要开展更多高质量、标准化的研究,明确不同饮食习惯对CD发病的相对贡献,为制定更精准的饮食干预策略提供依据。

2.2.2. 吸烟与CD发病风险

流行病学研究发现,吸烟是CD的独立危险因素。吸烟者相较于不吸烟者,发生CD的风险显著增加[29][30]。吸烟可通过多种机制促进CD的发生,如增加炎症介质的释放、破坏肠黏膜屏障、改变肠道微生物群等[31][32]。此外,吸烟还可诱导自由基的生成,引起氧化应激和DNA损伤。戒烟可显著降低CD的发病风险和复发率,改善疾病预后[33]。因此,戒烟被认为是改善CD患者预后的重要措施之一。

2.2.3. 生活方式与环境暴露

生活方式和环境暴露在CD的发生与发展中同样起着重要作用。研究表明,缺乏锻炼、肥胖和睡眠不足等均与CD的风险增加相关联[34]-[36]。规律的体育锻炼可改善CD患者的生活质量和预后[37]。此外,一些环境暴露因素如空气污染、药物使用、感染等也可能参与CD的发病过程[38][39]。例如,广谱抗生素的过度使用可导致肠道菌群失调,增加CD的发病风险[40]。总之,养成健康的生活习惯,减少有害环境暴露,对预防和控制CD具有重要意义。

2.3. 免疫系统的异常反应

2.3.1. 免疫细胞的功能失调

CD的发病与机体免疫系统的异常反应密切相关。研究发现,CD患者的固有免疫和适应性免疫细胞功能均存在紊乱[41]。巨噬细胞和树突状细胞等抗原呈递细胞对肠道微生物的识别和清除能力下降,导致病原菌持续刺激和炎症反应[42]。巨噬细胞表面存在多种模式识别受体(PRRs),如Toll样受体(TLRs)和NOD样受体(NLRs)。在正常生理环境下,这些受体可识别肠道微生物的特定分子模式,启动免疫反应,清除病原体。然而,在CD患者中,由于基因变异或环境因素影响,这些受体的表达或功能可能出现异常。例如,某些基因突变可能导致TLRs信号通路中的关键分子失活,使得巨噬细胞无法有效识别肠道微生物,从而不能及时启动免疫应答,导致病原菌在肠道内持续存在并刺激炎症反应[43]。此外,巨噬细胞分泌的促炎细胞因子如TNF- α 、IL-1 β 等增多,而抗炎细胞因子如IL-10分泌减少,进一步加剧了炎症反应[43]。

此外,CD患者的Th1和Th17细胞比例增高,而调节性T细胞(Treg)数量和功能减弱,促进了过度的炎症反应[44][45]。Th1细胞分泌IFN- γ 等细胞因子,激活巨噬细胞和细胞毒性T细胞,引起组织损伤。而Th17细胞则通过产生IL-17、IL-22等,招募中性粒细胞并加重炎症[46]。Th1、Th17和Treg细胞之间存在复杂的相互调节关系。Th17细胞分泌的IL-17可抑制Treg细胞的功能,使其无法有效发挥免疫抑制作用;而Treg细胞分泌的IL-10则可抑制Th17细胞的分化,减少IL-17等促炎细胞因子的产生。在CD患者中,这种平衡被打破,导致炎症反应失控[47]。

2.3.2. 炎症介质的释放与调节

CD的发生和发展伴随着多种炎症介质的异常释放与调节。肠道固有层中浸润的免疫细胞及上皮细胞可以分泌促炎细胞因子,例如TNF- α 、IL-1 β 和IL-6,这些因子的释放引发了炎症级联反应并导致组织

损伤[48]。其中, $\text{TNF-}\alpha$ 通过破坏肠上皮屏障而增加肠道通透性, 从而促进中性粒细胞的浸润[49]。IL-23 则刺激 Th17 细胞分化及 IL-17 的产生, 在 CD 的慢性炎症进程中发挥关键作用[9]。

2.3.3. 自身免疫机制的参与

尽管 CD 主要被视为一种自身炎症性疾病, 自身免疫机制在其发病中亦可能发挥一定作用。在部分 CD 患者的血清中检测到抗酵母抗体(ASCA)、抗中性粒细胞胞浆抗体(ANCA)等自身抗体, 提示自身免疫反应的参与[50]。此外, 部分 CD 患者还伴随其他自身免疫性疾病如银屑病、强直性脊柱炎等, 这提示两者在发病机制上可能存在相关性[51]。自身免疫疾病的特征在于免疫系统错误地将自身组织识别为外来物质并进行攻击, 这一过程通常与遗传易感性和环境因素的相互作用有关[52]。研究表明, 肠道微生物群的失调与自身免疫疾病的发生密切相关, 微生物的变化可能通过影响免疫耐受性和炎症反应而促进自身免疫机制的激活[53]。然而, 目前关于自身免疫在 CD 发病中作用的争议较大。一方面, 部分研究认为自身抗体是 CD 发病的始动因素, 这些抗体可能通过识别肠道上皮细胞或免疫细胞表面的特定抗原, 激活补体系统和免疫细胞, 引发炎症反应。另一方面, 也有观点认为自身抗体只是疾病进展过程中的伴随现象, 是肠道炎症导致组织损伤后, 自身抗原暴露引发的免疫反应[54]。因此, 自身免疫在 CD 发病中的确切作用尚需进一步研究和阐明。

2.4. 最新研究成果与未来方向

近年来, 研究发现 CD 患者肠道黏膜中 miRNA 的表达谱发生改变, 例如 miR-31 和 miR-146a 的上调与疾病活动性相关[55] [56]。蛋白质组学和代谢组学的研究也鉴定出一些潜在的生物标志物, 如粪钙卫蛋白(Fecal Calprotectin)和血清白细胞介素-6 (IL-6)水平与 CD 的病情相关[57] [58]。这些新兴生物标志物的发现不仅加深了对 CD 发病机制的理解, 也为疾病的精准诊断和个体化治疗提供了新的思路, 从而有望提高患者的生活质量和治疗效果。

精准医学基于个体的基因组、表观基因组、蛋白质组及代谢组信息, 同时结合临床表型数据, 以实现疾病的精准诊断、预后预测和个体化治疗[59]。在 CD 的治疗中, 精准医学的理念正在获得越来越多的关注与应用。例如, 有两项研究显示不同亚型患者对治疗的应答性存在差异, 这表明分子分型可用于预测治疗效果并指导精准用药[60] [61]。此外, 药物基因组学的研究也为 CD 的个体化用药提供依据, 例如 TPMT 和 NUDT15 基因多态性与硫唑嘌呤类药物的不良反应相关, 基因检测可指导药物剂量的调整[62]。同时, 临床医生也在探索如何通过影像学检查和生物标志物监测来评估治疗效果, 以便及时调整治疗方案, 减少不必要的副作用和治疗费用[63]。精准医学在 CD 治疗中的应用有望提升疗效、降低不良反应, 从而实现个体化治疗的目标。

3. 结论

尽管 CD 的发病机制和治疗策略研究取得了显著进展, 但仍面临诸多挑战。CD 的病因和发病机制错综复杂, 涉及遗传、环境、免疫及微生物等多个因素的相互作用, 尚未完全阐明[2] [64]。此外, CD 患者的临床表现和治疗反应存在显著个体差异, 现有治疗方法的疗效有限, 复发率高, 迫切需要开发新的治疗策略。未来 CD 的研究应进一步整合多组学数据, 深入解析疾病的分子机制, 并发现新的治疗靶点和生物标志物。此外, 肠道微生物群与 CD 发病的关系也是未来研究的重点方向之一, 益生菌、粪菌移植等微生态调节策略有望成为治疗 CD 的新手段[65]。总之, 尽管 CD 的研究仍面临诸多挑战, 但组学技术和精准医学的发展也为 CD 的防治带来了新的机遇, 未来的研究必将推动 CD 诊疗水平的不断提升。

参考文献

- [1] Dolinger, M., Torres, J. and Vermeire, S. (2024) Crohn's Disease. *The Lancet*, **403**, 1177-1191.

- [https://doi.org/10.1016/s0140-6736\(23\)02586-2](https://doi.org/10.1016/s0140-6736(23)02586-2)
- [2] Roda, G., Chien Ng, S., Kotze, P.G., Argollo, M., Panaccione, R., Spinelli, A., *et al.* (2020) Crohn's Disease. *Nature Reviews Disease Primers*, **6**, Article No. 22. <https://doi.org/10.1038/s41572-020-0156-2>
 - [3] Zhao, M. and Burisch, J. (2019) Impact of Genes and the Environment on the Pathogenesis and Disease Course of Inflammatory Bowel Disease. *Digestive Diseases and Sciences*, **64**, 1759-1769. <https://doi.org/10.1007/s10620-019-05648-w>
 - [4] Mirkov, M.U., Verstockt, B. and Cleynen, I. (2017) Genetics of Inflammatory Bowel Disease: Beyond NOD2. *The Lancet Gastroenterology & Hepatology*, **2**, 224-234. [https://doi.org/10.1016/s2468-1253\(16\)30111-x](https://doi.org/10.1016/s2468-1253(16)30111-x)
 - [5] Albenberg, L. (2023) The Role of Diet in Pediatric Inflammatory Bowel Disease. *Gastroenterology Clinics of North America*, **52**, 565-577. <https://doi.org/10.1016/j.gtc.2023.05.011>
 - [6] Elford, A.T., Ardalan, Z., Simkin, P. and Christensen, B. (2024) Comprehensive Review and Update of Stricturing Crohn's Disease. *Indian Journal of Gastroenterology*, **43**, 64-77. <https://doi.org/10.1007/s12664-023-01508-8>
 - [7] Hornschuh, M., Wirthgen, E., Wolfien, M., Singh, K.P., Wolkenhauer, O. and Däbritz, J. (2021) The Role of Epigenetic Modifications for the Pathogenesis of Crohn's Disease. *Clinical Epigenetics*, **13**, Article No. 108. <https://doi.org/10.1186/s13148-021-01089-3>
 - [8] Hugot, J., Chamaillard, M., Zouali, H., Lesage, S., Cézard, J., Belaiche, J., *et al.* (2001) Association of NOD2 Leucine-Rich Repeat Variants with Susceptibility to Crohn's Disease. *Nature*, **411**, 599-603. <https://doi.org/10.1038/35079107>
 - [9] Duerr, R.H., Taylor, K.D., Brant, S.R., Rioux, J.D., Silverberg, M.S., Daly, M.J., *et al.* (2006) A Genome-Wide Association Study Identifies *IL23R* as an Inflammatory Bowel Disease Gene. *Science*, **314**, 1461-1463. <https://doi.org/10.1126/science.1135245>
 - [10] Vuyyuru, S.K., Shackelton, L.M., Hanzel, J., Ma, C., Jairath, V. and Feagan, B.G. (2023) Targeting IL-23 for IBD: Rationale and Progress to Date. *Drugs*, **83**, 873-891. <https://doi.org/10.1007/s40265-023-01882-9>
 - [11] Takač, B. (2020) Interactions among Interleukin-6, C-Reactive Protein and Interleukin-6 (-174) G/C Polymorphism in the Pathogenesis of Crohn's Disease and Ulcerative Colitis. *Acta Clinica Croatica*, **59**, 67-80. <https://doi.org/10.20471/acc.2020.59.01.09>
 - [12] Strober, W. and Watanabe, T. (2011) NOD2, an Intracellular Innate Immune Sensor Involved in Host Defense and Crohn's Disease. *Mucosal Immunology*, **4**, 484-495. <https://doi.org/10.1038/mi.2011.29>
 - [13] Hampe, J., Franke, A., Rosenstiel, P., Till, A., Teuber, M., Huse, K., *et al.* (2006) A Genome-Wide Association Scan of Nonsynonymous SNPs Identifies a Susceptibility Variant for Crohn Disease in *Atg16l1*. *Nature Genetics*, **39**, 207-211. <https://doi.org/10.1038/ng1954>
 - [14] Parkes, M., Barrett, J.C., Prescott, N.J., Tremelling, M., Anderson, C.A., Fisher, S.A., *et al.* (2007) Sequence Variants in the Autophagy Gene *IRGM* and Multiple Other Replicating Loci Contribute to Crohn's Disease Susceptibility. *Nature Genetics*, **39**, 830-832. <https://doi.org/10.1038/ng2061>
 - [15] Ferguson, L.R., Huebner, C., Petermann, I., Gearry, R.B., Barclay, M.L., Demmers, P., *et al.* (2008) Single Nucleotide Polymorphism in the Tumor Necrosis Factor- α Gene Affects Inflammatory Bowel Diseases Risk. *World Journal of Gastroenterology*, **14**, 4652-4661. <https://doi.org/10.3748/wjg.14.4652>
 - [16] Glocker, E., Kotlarz, D., Boztug, K., Gertz, E.M., Schäffer, A.A., Noyan, F., *et al.* (2009) Inflammatory Bowel Disease and Mutations Affecting the Interleukin-10 Receptor. *New England Journal of Medicine*, **361**, 2033-2045. <https://doi.org/10.1056/nejmoa0907206>
 - [17] Chu, H., Khosravi, A., Kusumawardhani, I.P., Kwon, A.H.K., Vasconcelos, A.C., Cunha, L.D., *et al.* (2016) Gene-Microbiota Interactions Contribute to the Pathogenesis of Inflammatory Bowel Disease. *Science*, **352**, 1116-1120. <https://doi.org/10.1126/science.aad9948>
 - [18] Halme, L. (2006) Family and Twin Studies in Inflammatory Bowel Disease. *World Journal of Gastroenterology*, **12**, 3668-3672. <https://doi.org/10.3748/wjg.v12.i23.3668>
 - [19] Spehlmann, M.E., Begun, A.Z., Burghardt, J., Lepage, P., Raedler, A. and Schreiber, S. (2008) Epidemiology of Inflammatory Bowel Disease in a German Twin Cohort: Results of a Nationwide Study. *Inflammatory Bowel Diseases*, **14**, 968-976. <https://doi.org/10.1002/ibd.20380>
 - [20] Loddo, I. and Romano, C. (2015) Inflammatory Bowel Disease: Genetics, Epigenetics, and Pathogenesis. *Frontiers in Immunology*, **6**, Article 551. <https://doi.org/10.3389/fimmu.2015.00551>
 - [21] Ventham, N.T., Kennedy, N.A., Nimmo, E.R. and Satsangi, J. (2013) Beyond Gene Discovery in Inflammatory Bowel Disease: The Emerging Role of Epigenetics. *Gastroenterology*, **145**, 293-308. <https://doi.org/10.1053/j.gastro.2013.05.050>
 - [22] Hou, J.K., Abraham, B. and El-Serag, H. (2011) Dietary Intake and Risk of Developing Inflammatory Bowel Disease: A Systematic Review of the Literature. *American Journal of Gastroenterology*, **106**, 563-573. <https://doi.org/10.1038/ajg.2011.44>

- [23] Kostic, A.D., Xavier, R.J. and Gevers, D. (2014) The Microbiome in Inflammatory Bowel Disease: Current Status and the Future Ahead. *Gastroenterology*, **146**, 1489-1499. <https://doi.org/10.1053/j.gastro.2014.02.009>
- [24] Desai, M.S., Seekatz, A.M., Koropatkin, N.M., Kamada, N., Hickey, C.A., Wolter, M., *et al.* (2016) A Dietary Fiber-Deprived Gut Microbiota Degrades the Colonic Mucus Barrier and Enhances Pathogen Susceptibility. *Cell*, **167**, 1339-1353.e21. <https://doi.org/10.1016/j.cell.2016.10.043>
- [25] Jantchou, P., Morois, S., Clavel-Chapelon, F., Boutron-Ruault, M. and Carbonnel, F. (2010) Animal Protein Intake and Risk of Inflammatory Bowel Disease: The E3N Prospective Study. *American Journal of Gastroenterology*, **105**, 2195-2201. <https://doi.org/10.1038/ajg.2010.192>
- [26] Qin, X. (2012) Etiology of Inflammatory Bowel Disease: A Unified Hypothesis. *World Journal of Gastroenterology*, **18**, 1708-1722. <https://doi.org/10.3748/wjg.v18.i15.1708>
- [27] Levine, A., Wine, E., Assa, A., Sigall Boneh, R., Shaoul, R., Kori, M., *et al.* (2019) Crohn's Disease Exclusion Diet Plus Partial Enteral Nutrition Induces Sustained Remission in a Randomized Controlled Trial. *Gastroenterology*, **157**, 440-450.e8. <https://doi.org/10.1053/j.gastro.2019.04.021>
- [28] Xu, D., Peng, Z., Li, Y., Hou, Q., Peng, Y. and Liu, X. (2023) Progress and Clinical Applications of Crohn's Disease Exclusion Diet in Crohn's Disease. *Gut and Liver*, **18**, 404-413. <https://doi.org/10.5009/gnl230093>
- [29] Pedersen, K.M., Çolak, Y., Vedel-Krogh, S., Kobylecki, C.J., Bojesen, S.E. and Nordestgaard, B.G. (2021) Risk of Ulcerative Colitis and Crohn's Disease in Smokers Lacks Causal Evidence. *European Journal of Epidemiology*, **37**, 735-745. <https://doi.org/10.1007/s10654-021-00763-3>
- [30] Mahid, S.S., Minor, K.S., Soto, R.E., Hornung, C.A. and Galandiuk, S. (2006) Smoking and Inflammatory Bowel Disease: A Meta-analysis. *Mayo Clinic Proceedings*, **81**, 1462-1471. <https://doi.org/10.4065/81.11.1462>
- [31] Allais, L., Verschuere, S., Maes, T., De Smet, R., Devriese, S., Gonzales, G.B., *et al.* (2020) Translational Research into the Effects of Cigarette Smoke on Inflammatory Mediators and Epithelial TRPV1 in Crohn's Disease. *PLOS ONE*, **15**, e0236657. <https://doi.org/10.1371/journal.pone.0236657>
- [32] Berkowitz, L., Schultz, B.M., Salazar, G.A., Pardo-Roa, C., Sebastián, V.P., Álvarez-Lobos, M.M., *et al.* (2018) Impact of Cigarette Smoking on the Gastrointestinal Tract Inflammation: Opposing Effects in Crohn's Disease and Ulcerative Colitis. *Frontiers in Immunology*, **9**, Article 74. <https://doi.org/10.3389/fimmu.2018.00074>
- [33] To, N., Gracie, D.J. and Ford, A.C. (2016) Systematic Review with Meta-Analysis: The Adverse Effects of Tobacco Smoking on the Natural History of Crohn's Disease. *Alimentary Pharmacology & Therapeutics*, **43**, 549-561. <https://doi.org/10.1111/apt.13511>
- [34] Wang, X., Wu, J., Wang, Q., *et al.* (2016) Association between Physical Activity and Inflammatory Bowel Disease Risk: A Meta-Analysis. *Digestive and Liver Disease*, **48**, 1425-1431.
- [35] Rahmani, J., Kord-Varkaneh, H., Hekmatdoost, A., Thompson, J., Clark, C., Salehisahlabadi, A., *et al.* (2019) Body Mass Index and Risk of Inflammatory Bowel Disease: A Systematic Review and Dose-Response Meta-Analysis of Cohort Studies of over a Million Participants. *Obesity Reviews*, **20**, 1312-1320. <https://doi.org/10.1111/obr.12875>
- [36] Ananthakrishnan, A.N., Long, M.D., Martin, C.F., Sandler, R.S. and Kappelman, M.D. (2013) Sleep Disturbance and Risk of Active Disease in Patients with Crohn's Disease and Ulcerative Colitis. *Clinical Gastroenterology and Hepatology*, **11**, 965-971. <https://doi.org/10.1016/j.cgh.2013.01.021>
- [37] Shephard, R. (2016) The Case for Increased Physical Activity in Chronic Inflammatory Bowel Disease: A Brief Review. *International Journal of Sports Medicine*, **37**, 505-515. <https://doi.org/10.1055/s-0042-103157>
- [38] Ananthakrishnan, A.N., McGinley, E.L., Binion, D.G. and Saeian, K. (2011) Ambient Air Pollution Correlates with Hospitalizations for Inflammatory Bowel Disease: An Ecologic Analysis. *Inflammatory Bowel Diseases*, **17**, 1138-1145. <https://doi.org/10.1002/ibd.21455>
- [39] Ananthakrishnan, A.N. (2014) Environmental Risk Factors for Inflammatory Bowel Diseases: A Review. *Digestive Diseases and Sciences*, **60**, 290-298. <https://doi.org/10.1007/s10620-014-3350-9>
- [40] Shaw, S.Y., Blanchard, J.F. and Bernstein, C.N. (2010) Association between the Use of Antibiotics in the First Year of Life and Pediatric Inflammatory Bowel Disease. *American Journal of Gastroenterology*, **105**, 2687-2692. <https://doi.org/10.1038/ajg.2010.398>
- [41] Geremia, A., Biancheri, P., Allan, P., Corazza, G.R. and Di Sabatino, A. (2014) Innate and Adaptive Immunity in Inflammatory Bowel Disease. *Autoimmunity Reviews*, **13**, 3-10. <https://doi.org/10.1016/j.autrev.2013.06.004>
- [42] Smith, A.M., Rahman, F.Z., Hayee, B., Graham, S.J., Marks, D.J.B., Sewell, G.W., *et al.* (2009) Disordered Macrophage Cytokine Secretion Underlies Impaired Acute Inflammation and Bacterial Clearance in Crohn's Disease. *Journal of Experimental Medicine*, **206**, 1883-1897. <https://doi.org/10.1084/jem.20091233>
- [43] 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.
- [44] Sakuraba, A., Sato, T., Kamada, N., Kitazume, M., Sugita, A. and Hibi, T. (2009) Th1/Th17 Immune Response Is Induced by Mesenteric Lymph Node Dendritic Cells in Crohn's Disease. *Gastroenterology*, **137**, 1736-1745. <https://doi.org/10.1053/j.gastro.2009.07.049>
 - [45] Maul, J., Loddenkemper, C., Mundt, P., Berg, E., Giese, T., Stallmach, A., *et al.* (2005) Peripheral and Intestinal Regulatory CD4+CD25^{high} T Cells in Inflammatory Bowel Disease. *Gastroenterology*, **128**, 1868-1878. <https://doi.org/10.1053/j.gastro.2005.03.043>
 - [46] Strober, W. and Fuss, I.J. (2011) Proinflammatory Cytokines in the Pathogenesis of Inflammatory Bowel Diseases. *Gastroenterology*, **140**, 1756-1767.e1. <https://doi.org/10.1053/j.gastro.2011.02.016>
 - [47] Hovhannisyan, Z., Treatman, J., Littman, D.R. and Mayer, L. (2011) Characterization of Interleukin-17-Producing Regulatory T Cells in Inflamed Intestinal Mucosa from Patients with Inflammatory Bowel Diseases. *Gastroenterology*, **140**, 957-965. <https://doi.org/10.1053/j.gastro.2010.12.002>
 - [48] Neurath, M.F. (2014) Cytokines in Inflammatory Bowel Disease. *Nature Reviews Immunology*, **14**, 329-342. <https://doi.org/10.1038/nri3661>
 - [49] Noti, M., Corazza, N., Mueller, C., Berger, B. and Brunner, T. (2010) TNF Suppresses Acute Intestinal Inflammation by Inducing Local Glucocorticoid Synthesis. *Journal of Experimental Medicine*, **207**, 1057-1066. <https://doi.org/10.1084/jem.20090849>
 - [50] Mitsuyama, K. (2016) Antibody Markers in the Diagnosis of Inflammatory Bowel Disease. *World Journal of Gastroenterology*, **22**, 1304. <https://doi.org/10.3748/wjg.v22.i3.1304>
 - [51] Brakenhoff, L.K.P.M., van der Heijde, D.M., Hommes, D.W., Huizinga, T.W.J. and Fidder, H.H. (2010) The Joint-Gut Axis in Inflammatory Bowel Diseases. *Journal of Crohn's and Colitis*, **4**, 257-268. <https://doi.org/10.1016/j.crohns.2009.11.005>
 - [52] Rosenblum, M.D., Remedios, K.A. and Abbas, A.K. (2015) Mechanisms of Human Autoimmunity. *Journal of Clinical Investigation*, **125**, 2228-2233. <https://doi.org/10.1172/jci78088>
 - [53] Ni, J., Wu, G.D., Albenberg, L. and Tomov, V.T. (2017) Gut Microbiota and IBD: Causation or Correlation? *Nature Reviews Gastroenterology & Hepatology*, **14**, 573-584. <https://doi.org/10.1038/nrgastro.2017.88>
 - [54] Baumgart, D.C. and Carding, S.R. (2007) Inflammatory Bowel Disease: Cause and Immunobiology. *The Lancet*, **369**, 1627-1640. [https://doi.org/10.1016/s0140-6736\(07\)60750-8](https://doi.org/10.1016/s0140-6736(07)60750-8)
 - [55] Peck, B.C.E., Weiser, M., Lee, S.E., Gipson, G.R., Iyer, V.B., Sartor, R.B., *et al.* (2015) MicroRNAs Classify Different Disease Behavior Phenotypes of Crohn's Disease and May Have Prognostic Utility. *Inflammatory Bowel Diseases*, **21**, 2178-2187. <https://doi.org/10.1097/mib.0000000000000478>
 - [56] Polytaichou, C., Oikonomopoulos, A., Mahurkar, S., Touroutoglou, A., Koukos, G., Hommes, D.W., *et al.* (2015) Assessment of Circulating MicroRNAs for the Diagnosis and Disease Activity Evaluation in Patients with Ulcerative Colitis by Using the Nanostring Technology. *Inflammatory Bowel Diseases*, **21**, 2533-2539. <https://doi.org/10.1097/mib.0000000000000547>
 - [57] Sands, B.E. (2015) Biomarkers of Inflammation in Inflammatory Bowel Disease. *Gastroenterology*, **149**, 1275-1285.e2. <https://doi.org/10.1053/j.gastro.2015.07.003>
 - [58] Gecse, K.B., Brandse, J.F., van Wilpe, S., Löwenberg, M., Ponsioen, C., van den Brink, G., *et al.* (2015) Impact of Disease Location on Fecal Calprotectin Levels in Crohn's Disease. *Scandinavian Journal of Gastroenterology*, **50**, 841-847. <https://doi.org/10.3109/00365521.2015.1008035>
 - [59] Jameson, J.L. and Longo, D.L. (2015) Precision Medicine—Personalized, Problematic, and Promising. *New England Journal of Medicine*, **372**, 2229-2234. <https://doi.org/10.1056/nejmsb1503104>
 - [60] Weiser, M., Simon, J.M., Kochar, B., Tovar, A., Israel, J.W., Robinson, A., *et al.* (2016) Molecular Classification of Crohn's Disease Reveals Two Clinically Relevant Subtypes. *Gut*, **67**, 36-42. <https://doi.org/10.1136/gutjnl-2016-312518>
 - [61] Marigorta, U.M., Denson, L.A., Hyams, J.S., Mondal, K., Prince, J., Walters, T.D., *et al.* (2017) Transcriptional Risk Scores Link GWAS to EQTLs and Predict Complications in Crohn's Disease. *Nature Genetics*, **49**, 1517-1521. <https://doi.org/10.1038/ng.3936>
 - [62] Walker, G.J., Harrison, J.W., Heap, G.A., Voskuil, M.D., Andersen, V., Anderson, C.A., *et al.* (2019) Association of Genetic Variants in *NUDT15* with Thiopurine-Induced Myelosuppression in Patients with Inflammatory Bowel Disease. *JAMA*, **321**, 773-785. <https://doi.org/10.1001/jama.2019.0709>
 - [63] Mignini, I., Maresca, R., Ainora, M.E., Larosa, L., Scaldaferrri, F., Gasbarrini, A., *et al.* (2023) Predicting Treatment Response in Inflammatory Bowel Diseases: Cross-Sectional Imaging Markers. *Journal of Clinical Medicine*, **12**, Article 5933. <https://doi.org/10.3390/jcm12185933>
 - [64] Tamura, H. (2023) IgA Nephropathy Associated with Crohn's Disease. *World Journal of Methodology*, **13**, 67-78.

<https://doi.org/10.5662/wjm.v13.i3.67>

- [65] Sokol, H., Landman, C., Seksik, P., Berard, L., Montil, M., Nion-Larmurier, I., *et al.* (2020) Fecal Microbiota Transplantation to Maintain Remission in Crohn's Disease: A Pilot Randomized Controlled Study. *Microbiome*, **8**, Article No. 12.
<https://doi.org/10.1186/s40168-020-0792-5>