Advances in Clinical Medicine 临床医学进展, 2024, 14(3), 1418-1428
Published Online March 2024 in Hans. https://www.hanspub.org/journal/acm
https://doi.org/10.12677/acm.2024.143860

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炎症性肠病的生物标志物进展

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收稿日期：2024年2月27日；录用日期：2024年3月21日；发布日期：2024年3月27日

摘　要

炎症性肠病(inflammatory bowel disease, IBD)的发病率持续攀升，预计2025年我国IBD患者将达150万例，其诊断目前需要结合临床、实验室检查、影像学检查、内镜检查和组织病理学表现进行综合分析，血液与粪便来源的生物标志物侵入性低、可重复性高，在疾病诊疗的过程中起到重要的作用。本文对IBD生物标志物的应用现状、前沿新发现的生物标志物等方面的研究进行综述，总结目前研究在疾病诊疗中的应用，旨在更好地为临床应用提供参考，提高生物标志物诊疗的准确性。

关键词

生物标志物，溃疡性结肠炎，克罗恩病，炎症性肠病，代谢组学，蛋白质组学，实验室检查

Progress in Biomarkers of Inflammatory Bowel Disease

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Received: Feb. 27th, 2024; accepted: Mar. 21st, 2024; published: Mar. 27th, 2024

Abstract

The incidence of inflammatory bowel disease (IBD) continues to climb, and it is expected that the number of IBD patients in China will reach 1.5 million cases in 2025, and its diagnosis currently requires a comprehensive analysis combining clinical, laboratory examination, imaging, endoscopy and histopathological manifestations. Biomarkers of blood and faecal origin are less invasive

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文章引用: 陈舒, 廖璞. 炎症性肠病的生物标志物进展[J]. 临床医学进展, 2024, 14(3): 1418-1428.
DOI: 10.12677/acm.2024.143860

and more reproducible, and play an important role in the diagnosis and treatment of the disease. In this paper, we review the current status of IBD biomarkers and the newly discovered biomarkers, summarise the application of the current research in the diagnosis and treatment of IBD, and aim to provide a better reference for clinical application and improve the accuracy of biomarker diagnosis and treatment.

Keywords

Biomarkers, Ulcerative Colitis, Crohn's Disease, Inflammatory Bowel Disease, Metabolomics, Proteomics, Laboratory Tests

1. 背景

炎症性肠病(inflammatory bowel disease, IBD)是指原因不明的一组非特异性慢性胃肠道炎症性疾病，主要包括克罗恩病(Crohn's disease, CD)、溃疡性结肠炎(ulcerative colitis, UC)。随着经济发展的增强，进而环境风险因素、饮食习惯的改变、获得医疗水平、结肠镜检查等医疗技术的提升以及人口自然增长，IBD 的发病率将继续攀升，预计 2025 年我国 IBD 患者将达到 150 万例[1] [2]。IBD 的病因目前仍不明确，近年来的研究揭示其发病机制与宿主的遗传易感性、肠道微生物群、其他环境因素和免疫异常等相关[3]。早期诊断疾病并密切监测疾病的病变范围与疾病严重程度有助于 IBD 的治疗[4]。目前 IBD 的诊断缺乏金标准，主要是结合临床、实验室检查、影像学检查、内镜检查和组织病理学表现进行综合分析[5]。内镜检查的主要优势在于可以直观地观察肠道的不同段落，使得临床医生能够评估疾病的严重程度并监测其长期的活动情况，在一项由 618 名克罗恩患者组成的研究中表明，内窥镜是最不被接受的检查方式(VAS = 4.4 [1.2 - 7.3]) ($P < 0.0001$)，其主要原因包括结肠镜检查需要进行肠道清洁(76.3%)、直肠镜检查引起腹部不适(51.3%)，并且内镜检查价格昂贵、特别是可能会造成肠穿孔的风险[6] [7] [8]。实验室检查可重复性高，侵入性低，在临床中经常使用。生物标志物包含诊断生物标志物、检测生物标志物、药物反应生物标志物、预测生物标志物、预后生物标志物等多种类型[9]，在疾病诊断的多个阶段起到作用，例如初步诊断、疾病活动评估、治疗检测以及预测复发，从而提高 IBD 的诊断准确性和治疗效果。本综述我们将在回顾 IBD 中的生物标志物，以期更全面、更深入地了解 IBD 的生物学特征和进展。

2. IBD 中常用的生物标志物

2.1. 血液中常用的生物标志物

C-反应蛋白(C-reactive protein, CRP)与红细胞沉降率(erythrocyte sedimentation rate, ESR)是 IBD 诊断时血液中常用的生物标志物。

CRP 是一种急性期蛋白，它在全身炎症反应的急性期能够快速升高[10]，在人体发生炎症反应时，细胞释放的白细胞介素-6 (IL-6)能够促使肝脏合成 CRP [11]。Jin、Reena 和 Dan 等人的研究表明，在成人队列和儿童队列中均发现，CRP 的水平和疾病临床活动以及内窥镜活动有一定相关性，相较于 UC，活动期的 CD 中 CRP 升高得更明显，且不同疾病表型的 CD 患者的 CRP 水平没有差异[12] [13] [14]。一项来自挪威随访 5 年的研究表明，CD 患者 1 年后 CRP 水平升高，随后 4 年极有可能实施肠切除手术[15]。

CRP 也是反应药物治疗疾病效果的良好标志物，治疗 4 周后 CRP 恢复正常可以预测疾病在 5 年内缓解情况[16]。但是另一方面，由于 CRP 的非特异性，在自身免疫相关性疾病和心血管疾病发生时也会有升高的现象[17] [18]，导致对疾病监测结果的不准确。Arik 和 Craig 发现 CRP 水平与内窥镜、组织学和放射学疾病活动的相关性产生了相互矛盾的结果，多达三分之一的 IBD 患儿在诊断时 CRP 均正常[19] [20]。并且随着炎症部位增加，CRP 浓度相应上升但与炎症部位数量较少的组别差异并不明显[21]，有研究表明 CRP 升高可能是一种个体遗传性状，可能与个体的基因特征有关[22]。

ESR 是一种实验室测试，测量垂直试管中红细胞在重力作用下在 1 小时内沉降的距离[23]。1897 年波兰医生 Biernacki 发现了 ESR，并揭示了血沉的临床意义[24]，作为对炎症刺激反应缓慢的急性期蛋白的间接测量，当跟踪慢性炎症患者时，考虑使用血沉[25]。ESR 受多种复合因素的影响，如运动、吸烟、饮酒等生活方式[26]，冠心病的炎症、类风湿性关节炎、系统性红斑狼疮等疾病的 ESR 也会有不同程度的升高[27] [28]。在 IBD 中，研究表明 ESR 水平与疾病严重程度及疾病活动程度呈正相关[29]，ESR 可以反映 UC 的活动和疾病的严重程度，并在儿童队列中也得到验证[12]，并且 ESR 水平与 UC 患者的内镜活动指数中度相关[14]，较高的 ESR 预测了 CD 患者瘘管及肠道狭窄的发生[30]。

CRP 方便、快速、经济，经常作为 IBD 复查中的检查项目，是对 IBD 活动程度进行有效监测的指标，是一个很好的长期生物标志物，可通过反复测量来评估治疗效果。ESR 通常作为其他临床和实验室检查的补充，如结肠镜检查和组织活检，此外，ESR 还可以用于监测 IBD 患者的治疗效果，与 CRP 一起使用。但 ESR 敏感性和特异性较低，故当监测疾病活动性时时，应优先考虑 CRP [31]。

2.2. 粪便中常用的生物标志物

粪便钙卫蛋白(fecal calprotectin, FC)和粪便乳铁蛋白(fecal lactoferrin, FL)是 IBD 诊断时粪便中常用的生物标志物。

FC 是一种钙和锌结合的中性粒细胞胞浆蛋白，于 20 世纪 80 年代首次发现，由 S100A8 和 S100A9 两个亚基异质复合体形成，FC 浓度与机体的炎症的程度成正比[32] [33]。FC 可提供一种无创手段来筛查有肠应激综合征症状的 IBD 患者，IBD 与肠应激综合征有相似的临床表现，FC ≤ 40 μg/g 时，IBD 发生的概率 ≤ 1% [34]。较 CRP、WBC 等指标来说，FC 与疾病肠道炎症活检结果有更好的相关性[21]，FC 与内窥镜下疾病活动性高度相关并可作为预测儿童 CD 患者临床缓解和黏膜愈合的替代标志物[35] [36]。FC 同时可以预测疾病复发，Roblin 等人发现，TLI (<2 μg/ml)和 FC (>250 μg/g)的组合是预测疾病复发的良好模型[37]。

FL 是一种由粘膜分泌的铁结合糖蛋白，分子量约为 80,000 U，是中性粒细胞中发现的一种铁结合蛋白[38]。FL 具有铁结合/转移、抗菌、抗病毒、抗真菌、抗炎和抗致癌特性[39]，FL 在 IBD、阿尔茨海默病和干眼病等多种疾病的诊断中广泛应用，在肠道疾病中应用最为广泛[40] [41] [42]。Sunanda 和 Stacy 的研究表明 FL 与 IBD 的肠道炎症高度相关[34] [43]，FL 同样有助于区分 IBD 和肠易激综合征。多项对 IBD 患者在内窥镜检查后内对 FL 检测结果进行回顾性分析表明，FL 可用于区别疾病的严重程度，并与内镜下评密切相关[44] [45]。在一项大型长期随访研究中，FL 升高可预测 3 个月内 CD 和 UC 患者疾病复[46]，在肠切除的患者中，FL 在术后长期随访中仍会保持高水平，也可在术后随访期间预测疾病的复发[47]。

FC 较为稳定，便于检测，Anders 的研究表明，在室温下放置 3 天，FC 浓度变化不大[48]，故患者可以在家收集样本。由于粪便生物标志物与肠道黏膜直接接触，对比血清生物标志物来说，在确定胃肠道炎症时可能更准确，并且可以一定程度避免反复侵入性肠镜检查，但具有高敏感性和低特异性，肠道

的感染、HIV、新冠病毒的感染都可以引起 FC 的变化，因此，在诊断 IBD 之前，需结合 IBD 的临床表现，并排除粪便中 FC 浓度升高的其他原因。FL 水平较低时，可避免进一步检测肠镜。ESR 在怀孕期间会增高，儿童则不易进行内镜，故 FL 在一些情况下可以更好的预测疾病活动。

3. 近几年新发现的生物标志物

3.1. 外周血慢性炎症比值

许多研究发现外周血慢性炎症比率可能在 IBD 的临床实践中有一定的应用价值，这些比值无需额外的检查，易于获得。NLR (neutrophil-to-lymphocyte ratio)、CRP/ALB、PLR (platelet-lymphocyte ratio)、AGR (albumin/globulin ratio)、LMR (lymphocyte to monocyte ratio)可以将 IBD 患者从健康人中区分开[49] [50] [51] [52] [53]，并且与疾病的活动性关系密切。处于活动期的 IBD 患者的 NLR、CRP/ALB、PLR 水平显著高于非活动期 IBD 患者，AGR、LMR 低于非活动期 IBD 患者，对成人与儿童 UC 患者的研究中均发现 NLR 与 PLR 可作为判断疾病活动性的指标[54] [55]。CRP/ALB 可以预测 CD 患者的黏膜愈合，同时区分是否有肠穿孔情况[56]；CRP/ALB 同样能作为评估 UC 患者临床活性的潜在生物标志物[53] [57]。一项纳入 362 名 IBD 患者的研究发现 NPAR (neutrophil percentage-to-albumin ratio)和 AGR 在 IBD 和健康对照之间有很好的诊断价值，NPAR 水平在 IBD 患者患 CRC (结直肠癌)风险的预测可能起到作用[58]，并且无论在 UC 还是 CD 中，AGR 与疾病的临床活动性呈负相关[59] [60]。多项研究也表明 IBD 患者的单核细胞增多，LMR 降低可以预测 IBD 患者的疾病活动，并且可以在 3 个月内预测治疗情况[49] [61] [62]。

因为外周血慢性炎症比值是一个比率而不是绝对值，所以不会受到脱水或液体潴留等因素的影响，在临床实践中有着低成本和易获得的优势，与其他非侵入性标志物的组合是监测疾病活动可靠的指标。

3.2. 富亮氨酸 α-2 糖蛋白(Leucine -2 Glycoprotein, LRG)

富亮氨酸 α-2 糖蛋白(leucine -2 glycoprotein, LRG)是一种 50 kda 的糖蛋白，包含一个重复序列，带有一个富含亮氨酸的基序，不仅可以在肝细胞中表达，也可以在中性粒细胞、巨噬细胞和肠上皮细胞中表达[63]，近几年来有大量研究表明其与 IBD 疾病活动性相关。Eriko 等人发现，在 UC 患者中 LRG 可预测粘膜愈合，且在 CD 患者中 LRG 的表现与 CRP 和 FC 相当[64]。此外，LRG 还能够区分 CRP 水平正常但存在内窥镜活动的 UC 和 CD 患者的粘膜愈合情况[65]，在 Takahiro 等人的研究中得到了同样的结果，同时提出 LRG 可以替代 CRP 来评估 UC [66]。另一项研究表明，在 CD 患者中，当 LRG 临界值为 8.9 μg/ml，灵敏度为 93.3%；特异度为 83.3%，预测内窥镜缓解的曲线下面积为 0.904。Yasuda 等人在儿童队列中也评估了 LRG 水平，结果发现血清 LRG 可能比 CRP 更好地反映疾病活动性[67]，LRG 在 CD 患者较 UC 患者中更为适用。同时血清 LRG 还被证实与肠道狭窄相关[68]。综上，LRG 可作为预测 UC 和 CD 患者粘膜愈合的生物标志物，特别是对 CD 患者更具应用价值。

3.3. 内脏脂肪素(Visfatin)

内脏脂肪素(Visfatin)，是一种新发现的脂肪细胞因子，内脏脂肪素对应于一种之前被确定为 B 细胞群落增强因子(PBEF)的蛋白质[69]。其水平与多种代谢性疾病密切相关[70]。一项纳入 85 例初诊 IBD 患者及 30 例健康对照组的研究中，测定研究对象的血清内脂肪素、CRP、ESR 等生化指标。结果表明，IBD 组血清内脂肪素水平显著高于对照组，且内脂肪素与 CRP、ESR 和 FC 均呈现显著正相关。内脂肪素可作为诊断 UC 和 CD 的标志物[71]。Katarzyna 等人的研究同样也证实了血清内脏脂肪素在炎症性肠病中的应用。研究结果表明血清内脂肪素在活动期的 IBD 患者中较缓解期组的更高，血清内脂肪素 ≤ 1.54 ng/ml 为黏膜愈合的良好指标[72]。也有研究表明内脏脂肪素也可由中性粒细胞在炎症刺激下合成和释

放，并可作为多种炎症刺激导致的凋亡抑制剂。血清内脂肪素在 IBD 的静止期与缓解期表达均上调，反映了 IBD 的临床活性。因此，血清内脂肪素可能作为一种无创标志物，可用于 IBD 患者疾病诊断、活动监测。

3.4. 半乳糖素(Galectins)

半乳糖素(galectins)是一种半乳糖苷结合蛋白家族，通常在癌症和炎症等疾病的循环中发生改变[73]。一项研究采集 208 例 IBD 患者和 40 例健康人的血清样本，分析半乳糖凝集素-1、-2、-3、-4、-7 和-8 水平，评估其是否可作为 IBD 和 IBD 疾病活动的生物标志物。结果显示，IBD 患者血清中 galectin-1 和-3 水平明显高于健康人，而 galectin-2、-4、-7 和-8 水平则明显低于健康人，在截断值为 4.1 ng/ml 时，galectin-1 与健康对照组区分 IBD 的敏感性为 71%，特异性为 87% [74]。在该研究中，虽然没有半乳糖凝集素能够区分疾病的活动性，然而在另一项研究中表明 Galectin-1 在复发的患者中有所升高[75]。Galectin-1 (Gal-1)是一种内源性凝集素，具有关键的促溶解作用，包括诱导 T 细胞凋亡和分泌免疫抑制细胞因子[76]。对于 Galectin-1 是否能作为区分 IBD 活动性的生物标志物，可能需要在更大的队列进行进一步研究。D Cibor 等人的研究中发现 CD 患者的 Gal-3BP 中位水平明显高于对照组，然而 Gal-3、Gal-9 和 Gal-3BP 仍不能区分疾病的状态[77]。因此，虽然半乳糖凝集素不能区分活动性和非活动性 UC 和 CD，但其可与其他生物标志物联合使用作为 IBD 诊断的有用生物标志物。

4. 组学进展

4.1. 代谢组学生物标志物(Metabolomics)

代谢组学(Metabolomics)是一门新的研究技术，是一种对生物体内所有代谢物进行定量分析，并寻找代谢物与生理病理变化的相对关系的研究方式[78]。通过光谱和光谱技术，例如核磁共振(NMR)光谱或质谱(MS)，根据测试的生物标本的类型，可以发现各种代谢物。

几项研究表明，来自血清样本的一些代谢物可以将 IBD 患者从健康队列中成功分离。一项关于 IBD 的血清代谢组学研究中发现，由丙酮酸、苯乙酰谷氨酰胺、异石胆酸、牛磺去氧胆酸、糖乙醇胆酸组成的模型能够较准确地区分 CD 患者和 HC 患者，曲线下面积为 0.861 ($P < 0.001$)，并能将 IBD 从其他肠道疾病中区分开[79]。另外，越来越多的证据表明，IBD 患者的 TCA 循环受损，Stephens 和 Scoville 的研究中，IBD 与正常对照组相比，IBD 组 TCA 循环中间体显著减少，琥珀酸和乌头酸的水平明显降低，Schicho 的研究表明血清柠檬酸水平可以区分 CD 和 UC [80] [81] [82]。Daniluk 等人对 19 名新诊断 IBD 的患者的血清样本进行了分析，他们发现乳酸神经酰胺 18:1/16:0 (lacer)，可以用来鉴别 UD 与 CD 患者[83]。这些结果表示 IBD 患者的代谢紊乱，这些差异代谢物不仅可以鉴别疾病，还可以为疾病发病机制提供见解。同时，代谢组学也能发现生物标志物以评估疾病的活动性，粪便来自于肠道，更能体现于疾病活动性的关系。有研究探讨了 CD 患者粪便代谢物与疾病活动性之间的关系，在缓解期组中检测到较高浓度的粪便戊酸盐，而在活动期组中，粪便赖氨酸上调，另一项研究表明在 IBD 活动期间，粪便中短链脂肪酸水平降低[84] [85]。另一项研究中发现儿童 CD 患者的粪便尿囊素和谷氨酰基半胱氨酸，以及 UC 患者的粪便氨基己二酸、肌肽和 5-磷酸核糖与 FC 呈高度相关，是检测 CD 和 UC 内镜活动的敏感生物标志物[86]。

IBD 的病因复杂，代谢组学的应用可以发现更多的生物标志物以促进 IBD 患者的精确管理。关于 IBD 相关的代谢组学一般包括血清代谢组学和粪便代谢组学。据文献报道 IBD 患者对血液检测的接受程度远远高于肠镜与粪便检查[8]，近几年关于 IBD 血清代谢组学的研究也越来越多，在炎症性肠病的诊断、监测疾病进展、评估疾病活动性中起到重要作用。

4.2. 蛋白质组学的应用(Proteomics)

蛋白质组学(Proteomics)，是对蛋白质特别是其结构和功能的大规模研究，是在 90 年代初期，由 Marc Wikins 和学者们首先提出的新名词。各种技术已被用于分离和鉴定蛋白质种类，包括双向凝胶电泳、等电聚焦、生物质谱、飞行时间质谱、电喷雾质谱。

蛋白质组学研究已经帮助揭示了许多与 IBD 发病机制相关的宿主蛋白和途径，Skhoda 等人利用 MALDI-TOF 和 MS 鉴定出 UC 中膜联蛋白 A2 和程序性细胞死亡蛋白 8 参与肠上皮细胞(IECs)的稳态和破坏[87]；Zhao 等人鉴定出 p38 丝裂原活化蛋白激酶(MAPK)通路是 UC 中的分子标记[88]。蛋白质组学同样被应用来区分 IBD 患者与健康队列、IBD 患者的亚型，预测疾病的活动性。Yunki 等人研究使用非靶向 LC-MS/MS 定量蛋白质组学分析，在伴有肠道并发症的 CD 患者中发现上皮成分蛋白显著富集，并建立一个血清学生物标志物组，以将患有并发症的 CD 患者和无并发症的 CD 患者区分开来[89]。另一个针对儿童患者结肠活检的研究确定了两个候选生物标志物组，用于 IBD 的诊断和 IBD 亚型的分化，可指导儿童患者适当的治疗干预[90]，同样一组关于结肠活检的研究发现的生物标志物组模型同样能将 UC 与 CD 区分开来[91]，样本来源于结肠活检相较于血液的蛋白质组研究可能更容易将疾病进行分组。同时也可区分 UC 患者的不同时期，Kanmura S 等人建立了一个 22 例 CD 患者、48 例 UC 患者、5 例 CRC 患者、6 例感染性结肠炎患者和 13 例健康人的队列，分析血清以寻找能够正确反映疾病活动性的新的生物标志物。他们确定了三种蛋白(人中性粒细胞肽 1、2 和 3)，与其他所有组(包括非活性 UC 组)相比，活动性 UC 患者的血清水平更高[92]。使用蛋白质组学同时可以寻找生物标志物用于评估 IBD 对药物的治疗反应。一项研究调查了英夫利昔单抗和强的松对 IBD 患儿的治疗反应。该研究鉴定了对两种药物都有反应的 18 种蛋白质；其中一些随着炎症而下调，而另一些随着炎症的消除而上调，并发现炎症转录因子 NF-κB 调节的血清标志物是药效学生物标志物的潜在候选物，可对临床用药提供参考[93]。

蛋白质组学发现的 IBD 的生物标志物有助于发鉴定 IBD 患者表型及预测对治疗的反应，促进个性化医疗。通过不同的方法或在不同的实验室建立蛋白质组谱并不总是一致的。检测血清、结肠组织、粪便，随着采样位置不同所得到的研究结果也会不同。关于蛋白质组学在 IBD 中的应用仍需更多实验来进行验证。

5. 总结

目前 IBD 临床治疗终点的评定标准为内镜下黏膜愈合，已在 UC 和 CD 患者中被证明可以获得更优异的长期疗效。炎症标志物较临床症状更快速的反映疾病的活动度，较内窥镜侵入性更低。CRP、ESR 等常见生物标志物便宜可靠但不具备特异性，FC、FL 有着高灵敏度但患者接受程度差，外周血慢性炎症比值与一些新发现的生物标志物仍需进一步在更多队列进行验证，非侵入性采样具有最大的临床价值，随着代谢组学、遗传学和蛋白质组学的最新进展，现在有更多的工具可用来开发生物标记物来诊断 IBD。本文综述了近年来 IBD 中生物标记物的研究进展，需要更多的工作来帮助将这些新生物标志物与新技术应用到日常的临床实践中。

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