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表观遗传学在肠易激综合征发病机制中的研究进展

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摘 要

肠易激综合征(irritable bowel syndrome, IBS)发病机制复杂，目前尚未被完全阐明。近年来研究表明表观遗传学在IBS病理生理学中发挥重要作用，其包括DNA甲基化、组蛋白修饰、非编码RNA、染色质重塑。表观遗传学未来可能应用于IBS的诊断和治疗。本文就肠屏障功能、肠道炎症及免疫、肠道菌群、脑肠轴及内脏超敏反应、神经递质传导五方面论述表观遗传学在IBS病理生理学中的研究新进展。

关键词

肠易激综合征，表观遗传学，组蛋白去乙酰化酶(HDAC)，微小RNA

Research Progress on Epigenetics in Pathogenesis of Irritable Bowel Syndrome

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Abstract

The pathogenesis of irritable bowel syndrome (IBS) is complex and has not been fully elucidated. In

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recent years, studies have shown that epigenetics plays an important role in the pathophysiology of IBS, including DNA methylation, histone modification, non-coding RNA, and chromatin remodeling. Epigenetics may be applied to the diagnosis and treatment of IBS in the future. This article reviews the latest research advances in the role of epigenetics in the pathophysiology of IBS from five aspects: intestinal barrier function, intestinal inflammation and immunity, gut microbiota, gut-brain axis and visceral hypersensitivity, and neurotransmitter transmission.

Keywords

Irritable Bowel Syndrome (IBS), Epigenetics, Histone Deacetylase (HDAC), microRNA (miRNA)

1. 引言

肠易激综合征(irritable bowel syndrome, IBS)临床表现为排便习惯改变，粪便性状异常和腹痛、腹部不适症状，是临床最常见的功能性肠病，全球发病率约 4.1% [1]。根据《罗马 IV：功能性胃肠病》，IBS 分为四种亚型，腹泻型 IBS (diarrheal irritable bowel syndrome, IBS-D)、便秘型 IBS (Constipation-predominant Irritable Bowel Syndrome, IBS-C)，混合排便习惯 IBS (irritable bowel syndrome with mixed pattern, IBS-M)和未分类 IBS (irritable bowel syndrome unsubtyped, IBS-U) [2]。目前 IBS 发病机制尚未被完全阐明，近年来国内外研究表明 IBS 发病与肠屏障功能受损、肠道菌群失调、肠道免疫失衡，肠道低度炎症及神经内分泌失调等相关[3] [4]。表观遗传学指在不改变 DNA 序列的前提下，改变染色体、基因表达和遗传表型，包括 DNA 甲基化、组蛋白修饰，染色质重塑和非编码 RNA 表达(non-coding RNA, ncRNA) [5]。近年来，研究表明表观遗传学通过影响肠黏膜通透性、肠道菌群、肠道炎症及免疫、脑肠轴功能、内脏超敏反应等多方面参与 IBS 的发病[6]。本文将重点论述与 IBS 发病相关的表观遗传机制的最新发现，从而揭示 IBS 诊治的新靶点。

2. 肠屏障功能

肠黏膜屏障具有选择性通透性的特点，可避免有害抗原和细菌进入肠壁。近年来，国内外研究证实 IBS 患者存在肠黏膜屏障功能受损。研究显示，肠上皮组蛋白去乙酰化酶(histone deacetylase, HDAC) 1/2 缺乏会降低肠上皮细胞紧密连接蛋白 claudin-3 (CLDN3)的表达[7]。在小鼠肠道中敲低 HDAC1 和 HDAC2，会通过减少 CLDN3 基因启动子区域的组蛋白乙酰化水平，降低其转录活性，进而诱发肠上皮细胞损伤，破坏肠黏膜屏障完整性[8]。Wiley 等研究表明，白细胞介(interleukin, IL-6)可激活组蛋白甲基转移酶，促进组蛋白 3 赖氨酸 9 (H3K9me2/me3)甲基化，阻止转录因子 AP-1 与紧密连接(tight junction, TJ)基因启动子结合，降低 claudin-1 (CLDN1)表达，增加肠上皮通透性[9]。HDAC3 抑制剂可通过上调肠道节律基因 NFIL3，促进 NFIL3 与 ZO-1、CLDN1 基因启动子结合以增强其转录，修复肠黏膜屏障[10]。非编码 RNA (Non-coding RNA, ncRNA)表达异常与 IBS-D 患者肠屏障受损密切相关。结肠内 miR-199a/b 降低与肠易激综合征-D 患者的内脏疼痛相关，同样，大鼠背根神经节和结肠组织中 miR-199a 表达降低与内脏过敏性增强相关，体内 miR-199a 的上调通过抑制 TRPV1 信号减轻内脏疼痛[11]。因此，miR-199 前体可能是治疗内脏疼痛患者的有前景候选药物。IBS-D 患者肠上皮细胞中 lncRNA H19 表达降低，其通过结合水通道蛋白(aquaporin, AQP) 1/3 基因的转录抑制因子并阻断其作用，增加肠道通透性[12] [13]。IBS 患者中微

小 RNA-29 (microRNA 29, miR-29a)表达增加，靶向抑制 CLDN1、ZO-1mRNA，增加肠上皮通透性[14]。IBS-D 小鼠中，miR-144 高表达通过降解 ZO-1mRNA，减少紧密连接蛋白合成，破坏屏障完整性[15]。miR-21-5p 则通过干扰细胞骨架中微丝的聚合与重排，影响肠上皮细胞间的连接稳定性，改变肠道通透性[16]。相反，IBS-D 患者中 miR-16 和 miR-125b-5p 表达降低，会解除对其 IL-8 的转录抑制，IL-8 增加破坏紧密连接结构，引起肠道通透性升高[17]。

3. 肠道炎症及免疫

研究证实，肠道低度炎症及免疫失衡与 IBS 的发病及进展密切相关[18] [19]。研究表明，表观遗传学通过影响各类细胞因子来参与 IBS 的发病，主要包括白细胞介素、肿瘤坏死因子等。在感染后肠易激综合征(post-infectious irritable bowel syndrome, PI-IBS)结肠黏膜中，miR-510 表达下调，过氧化物还蛋白-1 表达上调，与肿瘤坏死因子-α (TNF-α)呈负相关，而抑制 miR-510 可使过氧化还原酶 1 (peroxiredoxin 1, PRDX1)表达上调，加重肠道炎症损伤[20]。在 IBS 动物模型中，miR-181c-5p 的过表达，使 TNF-α、IL-2 和 IL-6 的表达降低，抑制 IBS 大鼠肠道低度炎症[21]。而 IBS 患者性激素水平与免疫应答之间存在相互作用，雌激素受体 α 和 G 蛋白偶联雌激素受体在 IBS 中表达上调，细胞因子 IL-6、IL-10 和 TNF-α 及 miR-145、miR-148-5p 和 miR-592 表达紊乱[22]。HDAC1 和 HDAC2 缺失小鼠表现出肠道慢性炎症，由炎症分子表达特征和炎症基因表达改变决定。因此，HDAC1 和 HDAC2 通过调控肠道上皮细胞的增殖和分化，抑制肠道炎症反应[7]。此外，表观遗传学同时参与调节免疫细胞，参与 IBS 发病。IBS 患者肠黏膜肥大细胞数量明显增加，引起肠道低度炎症，诱发肠道免疫失衡[23]。miR-490-5 通过靶向类胰蛋白酶/PAR-2 信号通路促进肥大细胞增殖，影响肠道免疫[24]。IBS 患者肠道中的有机酸含量增加，其中丁酸钠作为 HDAC 抑制剂，选择性抑制传统树突状细胞(conventional dendritic cells, cDC2)，降低其刺激 T 细胞的能力，影响肠道免疫[25] [26]。国内学者研究显示丁酸盐抑制 IBS 大鼠 HDAC3 表达，降低 ERK 1/2 信号通路活化，调控肠系膜淋巴结树突状细胞免疫应答，减少 T 细胞增殖，抑制肠道免疫失调，改善 IBS 症状[27]。

4. 肠道菌群

近年来，IBS 宿主和肠道微生物之间的复杂关系得到了广泛研究。肠道微生物群通过其代谢产物调节肠道宿主的基因表达，进而受到宿主表观遗传调节[28]。肠道微生物群结构和丰度的改变致使 miRNA 谱变化，通过多种方式影响结肠上皮细胞[29]。国外学者通过研究确定多种微生物类群的丰度受宿主遗传学调控，其通过代谢产物影响宿主肠道上皮细胞的表观遗传状态，进而改变宿主新陈代谢方式[30]。发酵乳杆菌和唾液乳杆菌可通过激活肠上皮细胞内 TLR2/MyD88 信号通路，促进 miR-155 和 miR-223 的转录表达，分别靶向抑制促炎因子 TNF-α mRNA 的 3’UTR 区域及炎症相关蛋白 SOCS3 的编码序列，缓解肠道炎症，修复肠道屏障功能[31]。IBS 患者血液中 miR-199b 表达降低，与大肠杆菌数量呈负相关，而大肠杆菌过量增殖会通过分泌脂多糖激活肠上皮细胞的 NF-κB 通路，促进 miR-199b 的降解，从而解除对紧密连接破坏因子的抑制，导致肠道通透性升高[32]。IBS 患者厚壁菌门、放线菌门、粪杆菌门丰度显著异常，芽囊原虫可通过释放代谢产物吲哚乙酸激活肠上皮细胞 AHR 信号通路，调控 miRNA-16 的表达，miRNA-16 可靶向肠道动力相关蛋白的 mRNA，调节肠道蠕动功能，同时通过下调 IL-8 的表达，减少紧密连接结构破坏[33]。丁酸钠可通过抑制肠上皮细胞的 HDAC1/3 活性，增加紧密连接蛋白 CLDN3、ZO-1 基因启动子区域的组蛋白 H3 乙酰化水平，修复肠屏障，同时抑制结肠背根神经节中 HDAC2 活性，上调痛觉抑制因子 KCC2 的表达，降低内脏敏感性[34]。肠道菌群是短链脂肪酸的主要来源，后者通过激活肠道上皮细胞的 GPR41/43 受体，促进肠黏膜修复因子分泌，抑制小胶质细胞的过度激活，减少中枢神经

系统的痛觉信号[35]。肠道菌群参与消化可发酵寡糖、二糖和单糖以及多元醇(FODMAP)，低 FODMAP 饮食可降低肠道内渗透压，增加双歧杆菌、乳杆菌等益生菌的丰度，促进短链脂肪酸的产生，进而下调肠上皮细胞中 miR-29a 的表达，改善肠道屏障功能[36]。而厚壁菌门丰度增加会导致丁酸钠过量产生，激活肠嗜铬细胞的 TRPV1 通道，促进 5-HT 的释放，加速肠道蠕动，加重腹泻[37]。

5. 脑肠轴及内脏超敏反应

IBS 患者腹痛等症状可能是由外周对胃肠道刺激的敏感性增加所致，包括外周及中枢多种分子机制[38]。研究显示，IBS 患者交感迷走神经失衡、基础副交感神经张力降低，静脉注射促肾上腺皮质激素释放激素(corticotropin-releasing hormone, CRH)后，其促肾上腺皮质激素(Adrenocorticotropic hormone, ACTH)应答增强，激活肠黏膜神经节的 CRH-R1 受体，促进神经递质释放，同时激活中枢杏仁核 CRH 神经元，放大痛觉信号[39]。HDAC 抑制剂 MS-275 可通过抑制小鼠海马区 HDAC 1/2 活性，增加组蛋白 H3 乙酰化水平，促进脑源性神经营养因子(Brain-Derived Neurotrophic Factor, BDNF)转录，改善焦虑症状[40]。此外，动物模型中 BDNF 信号及糖皮质激素基因表达的上调，由组蛋白 H3K4me3 修饰介导[41]，而内脏超敏与脊髓组织组蛋白 4 赖氨酸 12 (H4K12)乙酰化减少相关，抑制 HDAC 可恢复 H4K12 乙酰化，促进脊髓背角痛觉抑制因子表达，减弱痛觉信号传递，逆转超敏反应[42]。另有研究发现，慢性应激可上调组蛋白乙酰转移酶 EP300，增加香草素亚型 1 (Transient Receptor Potential Vanilloid, TRPV1)启动子区组蛋白乙酰化，促进 TRPV1 转录，增加内脏敏感性，而敲低 EP300 可降低该乙酰化水平，抑制 TRPV1 表达，缓解应激性内脏疼痛[43]。杏仁核中央核内 HDAC 抑制可阻止应激诱导的 CRH 启动子组蛋白乙酰化，减少 CRH 合成；CRH 表达异常会通过脑肠轴激活外周肠神经，加重内脏超敏，为应激诱发 IBS 症状提供机制依据[44]。IBS 患者结肠中 BDNF 表达增加与腹痛和疾病严重程度呈正相关，与内脏敏感性参数呈负相关，其可能通过促进黏膜神经生长，增加内脏敏感性，参与 IBS-D 的发病机制[45]。日本有研究表明丁酸盐最有可能通过抑制 HDAC 导致巨噬细胞和肠神经胶质细胞释放高迁移率族蛋白 B1 (High mobility group box 1, HMGB1)，从而诱发小鼠结肠超敏反应，因此 HMGB1 及其受体可作为 IBS 患者结肠超敏反应的药物靶点[46]。

6. 神经递质传导

肠嗜铬细胞分泌的 5-羟色胺(5-HT)通过调控肠蠕动、神经传导维持肠道稳态，而其代谢失衡是 IBS 的核心病理特征之一。近年研究证实，表观遗传调控通过精准靶向 5-HT 受体功能、转运代谢及信号通路，参与调控 IBS 的病理进程。研究证实，5-HT 受体亚型的功能失衡是 IBS 分型的关键标志，5-HT3 受体过度激活与 IBS-D 的内脏高敏、肠道分泌亢进相关，而 5-HT4 受体功能不足则参与 IBS-C 的肠道动力减弱过程，二者均已成为临床治疗的核心靶点[47] [48]。而上述这种受体功能异常本质上受 miRNA 的转录后调控主导。研究证实，IBS-D 患者空肠黏膜中 miR-16 和 miR-103 显著下调，这两种 miRNA 可通过与 5-HT4 受体 mRNA 的 3’UTR 区域结合，抑制其翻译过程，从而加剧 IBS 症状[49]。HTR7 作为 5-HT 的 G 蛋白偶联受体，对内脏痛觉信号传导至关重要。IBS 患者结肠组织中 miR-29a 的过表达可直接靶向 HTR7 的翻译过程，导致受体蛋白水平降低，进而增强脊髓背根神经节对痛觉信号的敏感性，最终诱发内脏痛觉过敏[50]。5-HT 转运体(SERT)作为肠道 5-HT 清除的核心载体，其表达异常直接导致突触间隙 5-HT 蓄积或匮乏是 IBS 患者 5-HT 代谢紊乱的主要诱因[51] [52]。多项研究证实，不同 miRNA 通过协同调控形成表观遗传网络，精准控制 SERT 的表达水平：在 IBS-D 大鼠模型中，结肠黏膜的 miR-200a 显著上调，其通过降解 SERT mRNA 导致转运体蛋白减少，使肠道 5-HT 清除效率下降，过量 5-HT 激活肠平滑肌细胞上的受体，加速肠道转运引发腹泻[53]。在 IBS 患者和小鼠肠道黏膜上皮细胞中，miR-24 被上调，

检测显示 SERT 是 miR-24 的潜在靶基因，miR-24 抑制剂的提高了 IBS 小鼠近端结肠的疼痛阈值和伤害感受阈值水平，降低了髓过氧化物酶(Myeloperoxidase, MPO)活性，同时上调了肠道黏膜上皮细胞中 SERT 的 mRNA 和蛋白表达水平[54]。5-HT 系统不仅是表观遗传调控靶点，其自身也可通过介导组蛋白修饰，反向调控肠道稳态相关基因的表达。研究发现，5-HT 可通过激活转谷氨酰胺酶，诱导其与三甲基化组蛋白 4 (H4K3me3)发生共价结合，从而抑制肠道紧密连接蛋白转录，导致肠道通透性增加，同时，组蛋白修饰还与肠道内乳杆菌的丰度降低相关，而这类益生菌可通过代谢产物调节肠上皮细胞，进一步削弱肠道屏障功能与 5-HT 代谢平衡，加剧 IBS 症状[55]。

7. 小结和展望

近年来，国内外大量研究证实表观遗传学参与调控 IBS 的病理生理，这为进一步找到 IBS 诊治关键靶点提供实验基础。在诊断方面，miR-29a、miR-144 可作为 IBS 肠屏障受损标志物，其高表达与 ZO-1、CLDN1 下调及肠道通透性增加相关；miR-510 下调可提示 PI-IBS 肠道炎症，miR-16/miR-103 下调则关联 IBS-D 的 5-HT 代谢紊乱。在治疗方面，HDAC 家族潜力突出，HDAC 1/2 可调控肠上皮紧密连接蛋白，HDAC3 抑制剂能改善肠屏障与内脏高敏，丁酸盐作为 HDAC 抑制剂可调节肠道免疫，而 miRNA 调节剂如 miR-29a、miR-200a 拮抗剂，也有望改善 IBS 症状。然而，目前表观遗传学机制在 IBS 中的临床应用也存在局限性：一是组织特异性强，临床依赖结肠活检易致检测偏差；二是动物模型与临床患者的异质性，现有模型难以完全复现人类 IBS 的菌群–心理交互作用，靶点验证精确性不足；三是药物安全性待提升，非特异性 HDAC 抑制剂可能引发相关副作用，miRNA 调节剂存在脱靶风险，需研发相关靶向作用系统。未来研究可集中于利用单细胞测序等技术，解析 IBS 患者不同肠道细胞类型，例如肠上皮细胞、神经元细胞、免疫细胞等的表观遗传图谱，以寻找 IBS 更精准的治疗靶点。

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