OXFORD

Precision Clinical Medicine, 2023, **6**: pbad031

DOI: 10.1093/pcmedi/pbad031
Review

The significance of long non-coding RNAs in the pathogenesis, diagnosis and treatment of inflammatory bowel disease

Fei Jiang,[1,2] Min Wu,[3,4,*] Rongpeng Li [1,*]

[1]Jiangsu Province Engineering Research Center of Cardiovascular Drugs Targeting Endothelial Cells, School of Life Sciences, Jiangsu Normal University, Xuzhou 221000, China
[2]Department of Laboratory Medicine, the Affiliated Hospital of Xuzhou Medical University, Xuzhou 221000, China
[3]Drug Discovery Section, Wenzhou Institute, University of Chinese Academy of Sciences, Wenzhou 325000, China
[4]Department of Neurology, Medical College of Wisconsin, Milwaukee, WI 53226, USA
*Corresponding author. Rongpeng Li, Jiangsu Province Engineering Research Center of Cardiovascular Drugs Targeting Endothelial Cells, School of Life Sciences, Jiangsu Normal University, Xuzhou 221000, China. E-mail: lirongpeng@jsnu.edu.cn; Min Wu, Drug Discovery Section, Wenzhou Institute, University of Chinese Academy of Sciences, Wenzhou 325000, China. E-mail: miw100@ucas.ac.cn

Abstract

Inflammatory bowel diseases (IBD) are a group of chronic relapsing gastrointestinal inflammatory diseases with significant global incidence. Although the pathomechanism of IBD has been extensively investigated, several aspects of its pathogenesis remain unclear. Long non-coding RNAs (lncRNAs) are transcripts with more than 200 nucleotides in length that have potential protein-coding functions. LncRNAs play important roles in biological processes such as epigenetic modification, transcriptional regulation and post-transcriptional regulation. In this review, we summarize recent advances in research on IBD-related lncRNAs from the perspective of the overall intestinal microenvironment, as well as their potential roles as immune regulators, diagnostic biomarkers and therapeutic targets or agents for IBD.

Keywords: lncRNAs; inflammatory bowel diseases; intestinal barrier; intestinal microenvironment; immune regulator; diagnostic biomarker; therapeutic target

Introduction

Inflammatory bowel diseases (IBD) refer to a group of chronic relapsing gastrointestinal inflammatory disorders. Ulcerative colitis (UC) and Crohn's disease (CD) are the two major IBD subtypes [1]. The UC-associated inflammation is limited to mucosal layers of the colon and rectum, resulting in continuous superficial ulceration to the intestinal bowel wall [2]. In contrast, CD commonly involves the terminal ileum as well as the colon and presents different phenotypes, including stricture and penetration due to fibrosis and fistulas, respectively [3]. Abdominal pain and bloody diarrhea, weight loss, malnutrition, and fever are the most common IBD symptoms, whose diagnosis requires a combination of symptoms, endoscopy, histopathology, and laboratory tests [2, 3]. Due to its high prevalence in western countries and the recent significant increase in incidences in eastern countries, IBD is a huge global social and economic burden [4]. The exact pathogenesis of IBD has not been fully determined, however, multiple factors, including genetic background, environmental factors, and immune response dysregulation have been implicated [5]. Changes in any component of one of the above-mentioned factors are sufficient to induce IBD [6]. Intestinal immune system dysfunction-induced inflammatory changes are key precursors of IBD [7–10]. Besides, IBD occurrence and development are also regulated by complex environmental factors [11]. These risk factors can lead to intestinal barrier dysfunctions, which is central to IBD pathogenesis [12]. Thus, improving intestinal barrier function may be a potential therapeutic strategy for IBD. As a key pro-inflammatory cytokine, tumor necrosis factor (TNF) can cause barrier defects and inflammatory cascades, leading to prolonged disease course [13]. Anti-TNF treatment has been the mainstay of biologics in the last 20 years, with the ability to significantly restore intestinal barrier function and improve treatment outcome [14]. However, after cessation of treatment, a number of patients experience a relapse of inflammation [15]. The overall risk of relapse one year after discontinuation of anti-TNF therapy is 28% in UC and 40% in CD [16]. The lack of clarity in IBD pathogenesis and the difficulty in its treatment emphasizes the need to uncover the underlying causative mechanisms to facilitate the development of effective drugs.

Long non-coding RNAs (LncRNAs) are transcripts of longer than 200 nucleotides in length that have no evident protein-coding functions [17]. They participate in various biological processes, such as epigenetic modification regulation, function as transcriptional enhancers, recruitment of transcription factors, modification of protein translation or stability, and act as molecular sponges for miRNAs among others [18–22]. In IBD pathogenesis, lncRNAs are involved in microbial defense, mucosal barrier function regulation, intestinal epithelial restitution, innate and adaptive immune responses, and pathways associated with cellular homeostasis [1]. Given the significant role that lncRNAs play in

Received 18 September 2023; accepted 6 December 2023. **Published:** 11 December 2023

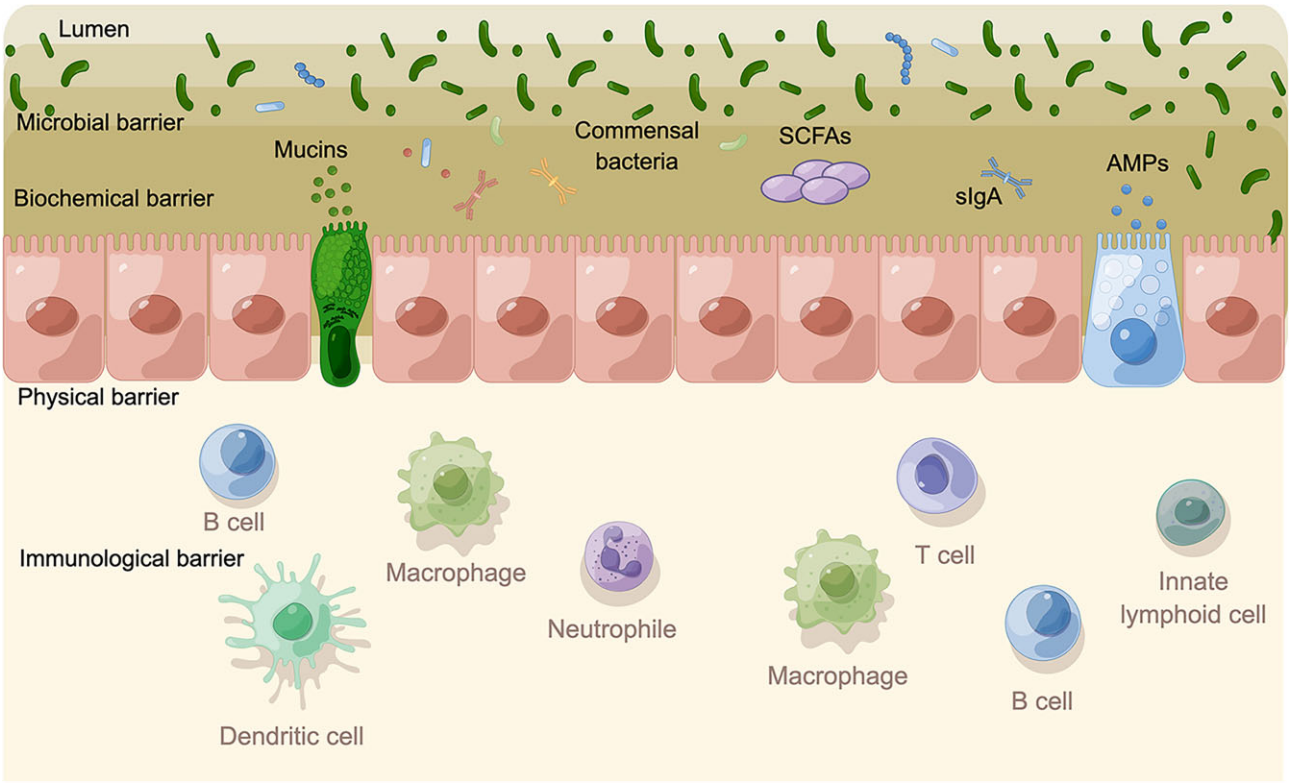

Figure 1. Structure of intestinal barriers. Intestinal homeostasis of a healthy body depends on four barriers. Beneficial bacteria in gut microbiota form an important microbial protective barrier against pathogens. Biochemical barriers include mucus, antimicrobial peptides, tissue repair factors, secretory IgA, and bacterial metabolites, all of which can inhibit the proliferation, adhesion and invasion of pathogenic bacteria. Physical barriers constitute intact intestinal mucosal epithelium, tight junctions, adhesive junctions and desmosomes between epithelial cells, which can effectively block bacteria, viruses and endotoxins. The immunological barrier is mainly composed of GALT and diffuse immune cells, which can recognize antigens in the intestinal environment, activate innate and adaptive immunity, resist invasion by pathogenic microorganisms, and suppress immune responses when necessary.

the pathogenesis of IBD, we consolidate the existing knowledge on the mechanisms and expression patterns of lncRNAs implicated in the initiation and advancement of IBD from the perspective of the overall intestinal microenvironment.

As for lncRNAs as biomarkers for diagnosis of IBD and drug targets for treatment, multiple reviews comprehensively analyzed the distinct in expression profiles of lncRNAs in both colonic tissues and plasma of patients with IBD using advanced techniques such as microarray or RNA sequencing, and highlighted the promising potential role of some lncRNAs as novel and valuable diagnostic biomarkers as well as promising therapeutic targets or drugs for IBD [23–25]. However, some existing problems have not been solved, such as sensitivity, specificity, consistency and stability for lncRNAs themselves, and experimental design flaws for researchers. We further put forward our own insights based on the above problems, with a goal of contributing to the clinical application and transformation of lncRNAs in the context of IBD.

Overview of intestinal barrier

The intestinal barrier consists of microbial, biochemical, physical and immunological barriers, which together play a role in maintaining the intestinal homeostasis (Fig. 1) [26]. Beneficial bacteria in the gut form an important microbial protective barrier against pathogens. Alterations in the composition of intestinal flora structure can pave the way for potential pathogens to colonize and invade the intestinal tract. This, in turn, triggers the release of inflammatory cytokines through interactions with host immune cells, ultimately exacerbating intestinal damage [27]. Biochemical barriers include the mucus, antimicrobial peptides, tissue repair factors (trefoil factors), secretory IgA, and bacterial metabolites, all of which can inhibit the proliferation, adhesion and invasion of pathogenic bacteria [28]. Physical barriers (mechanical barriers) refer to the intact intestinal mucosal epithelium and tight junctions, adhesive junctions and desmosomes between epithelial cells, which can effectively block bacteria, viruses and endotoxins [29]. Immunological barriers include gut associated lymphocyte tissues (GALT) and diffuse immune cells. The intestinal immune system can recognize antigens (bacteria, viruses, toxins) in the intestinal environment, activate innate and adaptive immunity, eliminate antigens, and effectively resist pathogenic invasion while suppressing immune responses when necessary to balance immune defense and maintain homeostasis [30]. IBD stems from structural changes in intestinal flora, abnormal immune responses, as well as damage to intestinal biochemical and physical barriers. In many of these biological processes, lncRNAs play a key role.

Functional mechanism of lncRNAs and its regulatory roles in IBD

Studies have shown that lncRNAs can regulate gene expression through diverse mechanisms involving following methods: signal, decoy, guide, scaffold, post-transcriptional regulation, and protein coding, thus modulating important biological processes (Fig. 2)

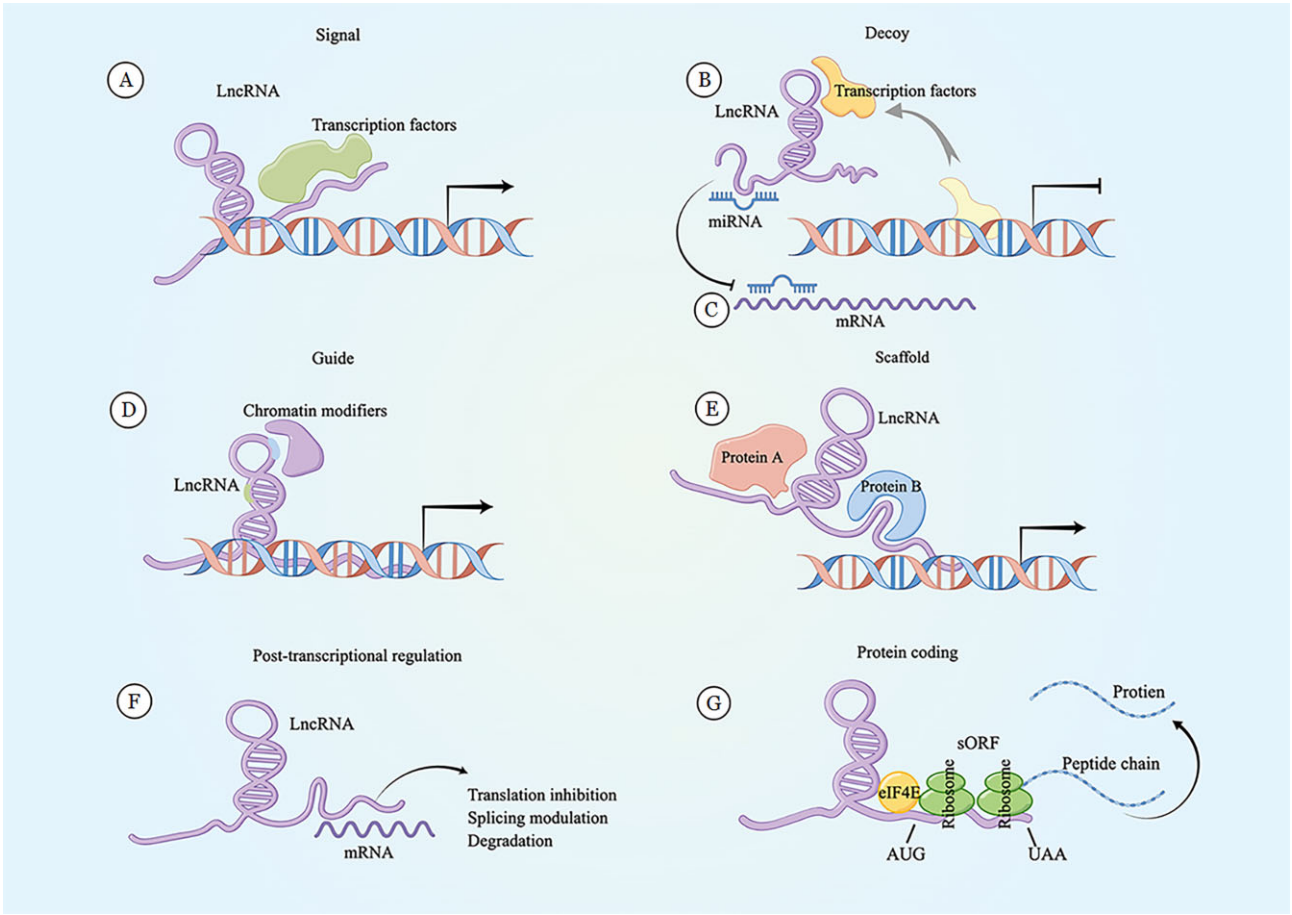

Figure 2. Mechanisms of lncRNA function. (A) As signals, lncRNAs directly interact with transcriptional factors to indicate gene regulation. (B) As decoys, lncRNAs can titrate away transcription factors away from chromatin, blocking effects of transcriptional factors. (C) lncRNAs act as decoys for miRNA target site, titrating miRNAs away from their mRNA targets and indicating mRNA expression. (D) As guides, lncRNAs can recruit chromatin modifying enzymes to target genes, either in *cis* or in *trans* to distant target genes. (E) As scaffolds, lncRNAs can bring together multiple proteins to form ribonucleoprotein complexes. (F) For post-transcriptional regulation, lncRNAs directly modulate processing of their mRNA targets at multiple levels, including translation, splicing and degradation. (G) For protein coding, eIF4E recognizes sORF on lncRNA to recruit ribosomes and initiate translation.

[17, 20, 31]. The first archetype of lncRNAs is "signal". LncRNAs are transcribed in a spatiotemporal manner in response to developmental cues, diverse stimuli, or cellular context. They actively participate in the specific signal pathways as molecular signals. The second function of lncRNAs is that of acting as decoy. LncRNAs act as a "molecular sink" for RNA-binding proteins. Certain lncRNAs function as miRNA decoys by binding to complementary sites on the coding sequences or 3' UTRs of target gene transcripts. Through this interaction, they indirectly regulate protein expression from specific mRNAs [32, 33]. The third action mode of lncRNA is the guide. LncRNAs interact with RNA binds protein(s), then direct the localization of ribonucleoprotein complex to specific targets. Furthermore, lncRNAs can function as molecular scaffold to recruit multiple effector partners (such as repressive and activated chromatin modifiers), thereby repressing or activating target gene expression, respectively. In addition, lncRNAs directly modulate the processing of their mRNA targets at post-transcriptional levels, including translation [34], splicing [35] and degradation [36]. Importantly, recent studies have found that numerous short or small ORFs (sORFs or smORFs) on lncRNAs have ability to encode peptides [37–41]. These translation products serve as novel potential prognostic biomarkers and therapeutic targets for the diagnosis and treatment of diseases.

Based on the molecular mechanism of lncRNAs mentioned above, lncRNAs are involved in IBD processes by regulating microbial defense, mucus barriers, intestinal epithelial restitution, innate and adaptive immune responses (Table 1).

LncRNAs regulate gut microbial defence

Establishing and sustaining beneficial interactions between the host and commensal microbiota are crucial factors for maintaining host health. Commensal microbiota inhabits virtually all host mucosal surfaces, with the majority residing within the gastrointestinal tract. There are thousands of bacterial species of four major bacterial phyla (*Firmicutes*, *Bacteroidetes*, *Proteobacteria* and *Actinobacteria*) in the whole human gut microbiome [42]. Gut microbiome composition or species diversity in the gut varies with diet, age, and drug factors among others [43]. In healthy intestines, the phyla *Bacteroidetes*, *Firmicutes*, *Actinobacteria*, *Proteobacteria*, and *Verrucomicrobia* predominate, and play a role in the production of epithelial metabolites [44]. In CD, the microbiota showed a significant decrease in the abundance of *Firmicutes* and *Bacteroidetes* and an increase of *Enterobacteria*. Reduced *Clostridium spp.* and increased *Escherichia coli* abundance have been reported in UC [45], resulting in increased intestinal colonization by infectious pathogens. The abundance of *Roseburia*

Table 1. Known mechanisms of lncRNAs involved in regulation of UC and CD.

LncRNAs	Sample	Targets	Biological function	Reference
Up-regulated in UC				
DANCR	Animal model	miR-125b-5p	Promote inflammation and down-regulate protective proteins level	[66]
CCAT1	Clinical sample (Colonic tissue)	miR-185–3p/MLCK	Up-regulate MLCK and further increase barrier permeability	[74]
H19	Clinical sample (Colonic tissue)	miR-675–5p/VDR	Decrease vitamin D receptor and TJ proteins expression, resulting in the epithelial barrier dysfunction	[75]
H19	Animal model	miR-675/ZO-1 and E-cadherin	Destabilize and repress the translation of ZO-1 and E-cadherin mRNAs, resulting in destruction of intestinal epithelial barrier function	[76]
H19	Animal model	miR-141/ICAM-1, miR-139/CXCR4	Up-regulate the expression of ICAM-1 and CXCR4 targeting miR-141 and miR-139, thus enhancing the immunosuppressive and promoting cell proliferation and migration	[109]
H19	Animal model	miR-331–3p/TRAF4	Promote TRAF4 transcription, thereby aggravating intestinal injury	[110]
NEAT1	Animal model	ZO-1, Claudin-5 and Occludin	Promote the inflammatory response by modulating the intestinal epithelial barrier and through exosome-mediated polarization of macrophages	[78]
NEAT1	Clinical sample (Colonic tissue)	TNFRSF1B/NF-κB p65	Promote NF-κB p65 translocation and mediate intestinal inflammation	[87]
NEAT1	Clinical sample (Colonic tissue)	miR-603/FGF9	Inhibit cell viability, and enhance cell apoptosis and the production of cytokines	[94]
NEAT1	Animal model	miR-204–5p/PI3K-Akt	Increase release of inflammation cytokines	[97]
NEAT1	Clinical sample (Colonic tissue)	miR-410–3p/LDHA	Enhance IECs dysfunction by breaking the homeostasis of the glucose metabolism	[101]
ITSN1-2	Clinical sample (Colonic tissue and PBMCs)	miR-125a/IL-23R	Promote $CD4^+$ T cell activation, proliferation, and Th1/Th17 cell differentiation, and increased inflammatory cytokines	[140]
ANRIL	Clinical sample (Colonic tissue)	miR-323b-5p/TLR4/MyD88/NF-κB	Promote cell apoptosis and cytokine production	[84]
NORAD	Clinical sample (Colonic tissue)	miR-552–3p/MYD88	Increase cell apoptosis, inflammation, and oxidative stress	[85]
IFNG-AS1	Clinical sample (Colonic tissue)	NF-κB, PI3K/Akt	Enhance inflammation and increase cell apoptosis	[88,89]
PINT	Clinical sample (Colonic tissue)	p65/EZH2/TNF-α	Act as a modular scaffold of p65 and EZH2 to coordinate their localization and specify their binding to the target genes (TNF-α)	[91]
NAIL	Clinical sample (Colonic tissue)	Wip1/p38/NF-κB	Inactivating Wip1 and further active NF-κB subunit p65, increasing proinflammatory cytokines	[92]
MALAT1	Clinical sample (Colonic tissue and plasma)	LncRNA ANRIL/PI3K-AKT pathway	Promote the apoptosis of colonic epithelial cells	[93]
SNHG5	Clinical sample (Colonic tissue)	miR-375/JAK2	Suppress cell proliferation and promote cell apoptosis	[108]
CRNDE	Cell model	miR-495/SOCS1	Promote colonic epithelial cell apoptosis	[111]
KIF9-AS1	Clinical sample (Colonic tissue)	miR-148a-3p/SOCS3	Enhance the colon injury and inflammation and increase the apoptosis colonic cells	[112]
BC012900	Clinical sample (Colonic tissue)	PPM1A/TP53-p53	Up-regulate PPM1A, which in turn activate the expression of tumor suppressor gene TP53/p53, leading to G2/M cell cycle arrest and apoptosis	[116]
OIP5-AS1	Animal model	miR-26a-5p/IL-6	Increase IL-6 expression	[147]
Down-regulated in UC				
PlncRNA1	Cell model	miR-34c-5p/MAZ/ZO-1	Inhibit the expression of MAZ, ZO-1, and occludin to destroy intestinal epithelial barrier integrity	[77]
CDKN2B-AS1 (ANRIL)	Clinical sample (Colonic tissue)	Claudin-2	Decreased colonic barrier integrity	[79]
MEG3	Animal model	miR-20b-5p/CREB1	Decrease cell viability and increase inflammatory responses	[25]
MEG3	Animal model	miR-98–5p/IL-10	Increased ROS, inflammatory cytokine production and promote cell apoptosis and pyroptosis	[105]

Table 1. (*Continued*)

LncRNAs	Sample	Targets	Biological function	Reference
ANRIL	PBMCs and serum	NF-κB	Increase inflammatory cytokine production and inflammation	[99]
CDKN2B-AS1	Clinical sample (serum)	miR-195–5p miR-16–5p	Promote cell apoptosis and increase inflammation response	[100]
78 583	Clinical sample (colon tissue)	miR3202/HOXB13/IL-10	Increase inflammation response	[88]
GAS5	Clinical sample (Colonic tissue)	MMP2/MMP9, Krüppel-like factor 2	Increase inflammatory damage	[90]
Mirt2	Clinical sample (plasma)	MAPK/IL-22	Decrease IL-22 expression and increase apoptotic rate of colonic epithelial cells	[98]
TUG1	Clinical sample (Colonic tissue)	miR-142–5p/SOCS1	Enhance cell injury and inflammation	[102]
TUG1	Animal model	HuR/c-mycmiR-29b-3p/CDK2	Suppress cell proliferation and promote cell apoptosis	[104]
PMS2L2	Clinical sample (plasma)	miR-24	Up-regulate miR-24 via methylation to promote cell apoptosis	[115]
Gm31629	Clinical sample (Colonic tissue)	YB-1/E2F	Suppress cell proliferation and epithelial regeneration	[117]
Up-regulated in CD				
DQ786243	PBMCs	CREB, Foxp3	Regulate the function of Treg through CREB and Foxp3	[143]
CNN3-206	Clinical sample (colonic tissue)	miR-212/Caspase10	Increase apoptosis, migration and invasion of intestinal epithelial cells	[114]
01 272	Clinical sample (colonic tissue)	miR-153–5p	Activate the epithelial-mesenchymal transition (EMT), causing the loss of epithelial cells and increases tissue damage	[116]
Down-regulated in CD				
MALAT1	Clinical sample (colonic tissue)	miR-146b-5p/NUMB/CLDN11	Destroy intestinal mucosal barrier and intestinal homeostasis	[80]
LOC102550026	Animal model	miRNA-34c-5p/Pck1	Increase reactive oxygen species and proinflammatory cytokines, and contributed to M1 polarization	[148]

PBMCs: Peripheral blood mononuclear cells.

intestinalis (R. intestinalis), one of the dominant intestinal commensal microbiotas, was found to be decreased in both UC and CD patients. *R. intestinalis*-derived flagellin ameliorates IBD colitis by suppressing inflammatory responses via inhibiting miR-223–3p-mediated activation of the NOD-like receptor protein 3 (NLRP3) inflammasome and production of pro-inflammatory cytokines [46]. Butyrate secreted by *R. intestinalis* enhances the binding of transcription factor specificity protein 3 (Sp3) to TLR5 promoter regions, up-regulating TLR5 transcription, protecting against microbial infections, inflammation, tissue injury and colitis [47]. Moreover, *R. intestinalis* increases ZO-1 protein expression [48] and stimulates thymic stromal lymphopoietin (TSLP) production in intestinal epithelial cells (IECs) via TLR5, inducing the secretion of IL-10 and TGF-β by dendritic cells (DCs), which promotes anti-inflammatory regulatory T cells (Tregs) differentiation to inhibit inflammation [49]. Targeted colonization by magnetic nanoparticle internalized *R. intestinalis* has been developed as a novel therapeutic strategy against colitis [50]. lncRNAs was found to regulate *R. intestinalis* flagellin-mediated alleviation of colitis. *R. Intestinalis* flagellin activated lncRNA HIF1A-AS2 promotor via increasing Stat1 phosphorylation, promoting Stat1 nuclear translocation, thereby activating promotor of HIF1A-AS2. Elevated HIF1A-AS2 inhibited inflammatory responses induced by flagellin in Dextran Sulfate Sodium (DSS) treated animals by inactivating the NF-κB/JNK pathway, suggesting that as a negative regulator of inflammatory responses, HIF1A-AS2 may be a novel therapeutic agent for colitis [51]. It was reported that lncRNA NKILA bound to NF-κB/IκB, and directly masked the phosphorylation motifs of IκB, thereby inhibiting IKK-induced IκB phosphorylation and NF-κB activation [52]. Whether HIF1A-AS2 can also bind to NF-κB/IκB complex and inhibit NF-κB signaling by masking the phosphorylation sites of IκB and stabilizing the complex needs to be further investigated. Microarray analysis of mice colonic endothelial cells treated with DSS and flagellin showed significant up-regulation of 1206 lncRNAs and down-regulation of 628 lncRNAs [51]. These findings establish a comprehensive database for investigating the regulatory impact of lncRNAs on IBD, particularly concerning the defense against intestinal commensal bacteria.

Neonatal necrotizing enterocolitis (NEC), a serious inflammatory bowel disease of newborns, has multifactorial etiopathogenesis. The abundance of *Fusobacterium nucleatum* (*F. nucleatum*) in NEC patients is higher than in healthy individuals [53]. In mice models, *F. nucleatum* aggravated colitis, increased MPO activity levels, and promoted the secretion of pro-inflammatory cytokines in colon tissues. Mechanistically, *F. nucleatum* selectively activated lncRNA ENO1-IT1 transcription via upregulating the binding efficiency of transcription factor SP1 to the promoter region of ENO1-IT1, inducing IRF5 mRNA and protein expression through sponging miR-22–3p, further increasing the expression of various inflammatory cytokines, and aggravating colitis [54]. Thus, lncRNA ENO1-IT1 is an important target for *F. nucleatum* in NEC-associated inflammation. Hong et al. reported that *F. nucleatum* promoted

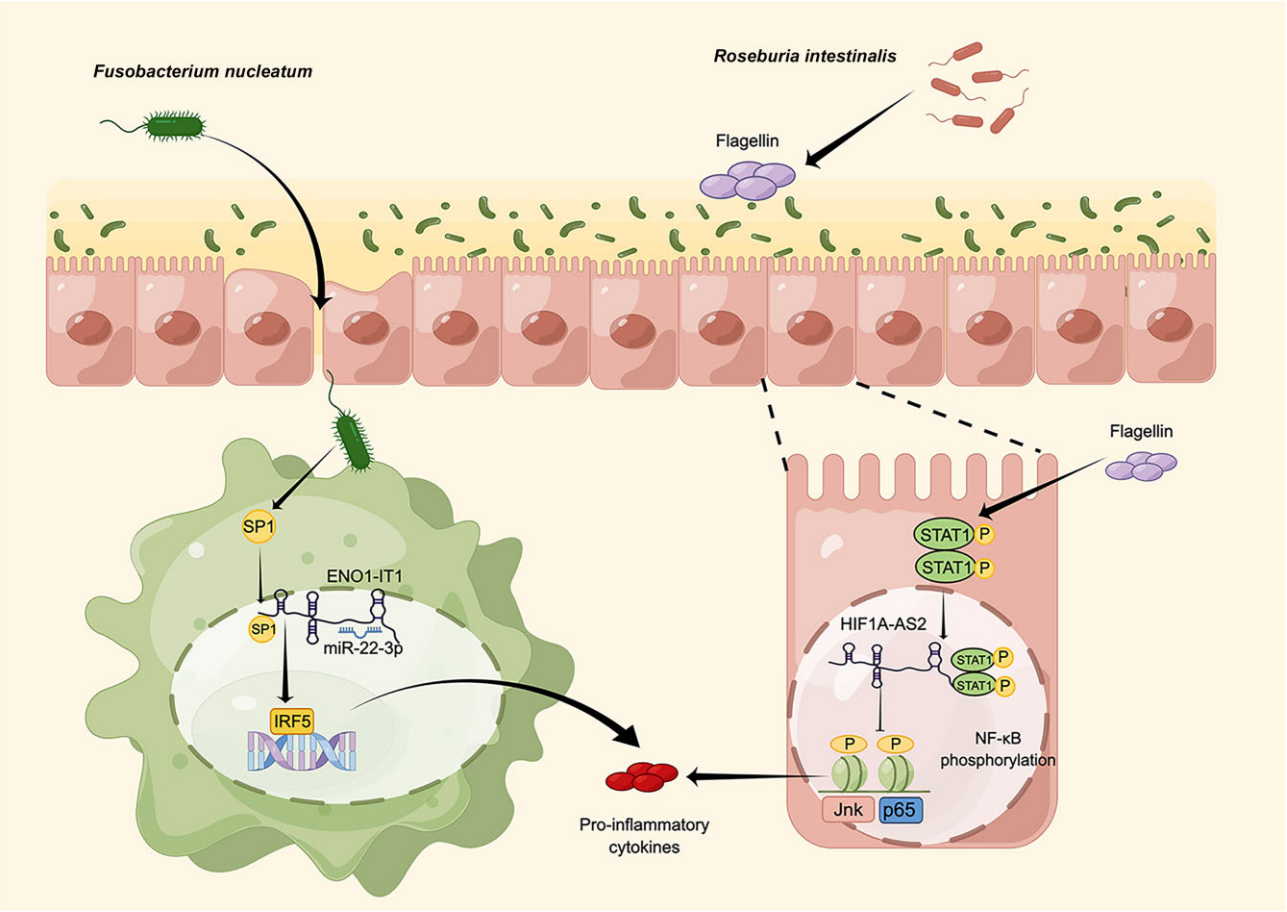

Figure 3. Intestinal commensal bacteria target lncRNAs to regulate immune responses and affect intestinal homeostasis. LncRNA ENO1-IT1 and IRF5 can form competing endogenous RNA (ceRNA) networks and crosstalks occur through shared miR-22–3p. LncRNA HIF1A-AS2 can target transcriptional regulators (NF-κB) to regulate related molecular signaling pathways.

glycolysis and tumorigenesis of colorectal cancer by targeting ENO1-IT1 [54]. These findings show that intestinal commensal bacteria can target lncRNAs to regulate immune responses, which alters the intestinal homeostasis (Fig. 3).

Microbial organisms and their products can affect the host's mucosal barrier function and immune responses to commensal microbes. To date, several studies have explored the relationship between intestinal microbial composition and lncRNAs expression profiles [55–57]. Liang et al. conducted a study where they observed distinct lncRNA expression profiles in intestinal tissues that enabled the differentiation of germ-free mice from mice re-colonized with various types of microorganisms. These findings strongly suggest that lncRNA expression profiles hold promise as an effective tool for distinguishing and characterizing different microbial compositions in the gut [56]. Therefore, we believe that the altered intestinal microbial composition in IBD will cause changes in the lncRNA expression profile of intestinal tissue. This is also confirmed by another study [55]. Braun et al. used hierarchical All-against-All association testing (HAllA) to identify specific significant associations between lncRNAs and microbial abundance Amplicon Sequence Variants (ASVs) in UC. The data revealed positive association between lncRNA GATA6-AS1 and *Blautia*, between lncRNA LINC01272 and *Streptococcus* and *Veillonella*, and a negative association between GATA6-AS1 and *Enterococcus*. Furthermore, the researchers observed that the decreased expression of lncRNA HIF1A-AS2 in the gut epithelium of mice resulted in heightened susceptibility to DSS-induced colitis. This susceptibility was concomitant with significant changes in the composition of gut microbiota. On the other hand, the presence of lncRNA HNF1A-AS1 played a crucial role in preserving the integrity of the intestinal mucosal barrier. Reduced expression of HNF1A-AS1 led to more severe mucosal injury, consequently causing alterations in the microbial community [51].

In summary, the intricate interplay between microbial abundance and mucosal lncRNA expression play a critical role in preserving intestinal homeostasis. However, the precise mechanisms through which microbial signals influence the regulation of lncRNA expression require further in-depth investigation.

LncRNAs regulate mucosal biochemical and physical barriers

Evidence has indicated that intestinal homeostasis is influenced not only by the gut microbiota composition, but also by microbial products. Gut microbiota and their products can not only induce the production of secretory IgA (sIgA) [58] and antimicrobial peptides (AMPs) [59, 60], but also stimulate the release of mucins [61], which constitute the biochemical barrier of the intestine. Mucins are produced by goblet cells and secreted into the intestinal lumen. Based on their structure and localization, mucins can be divided into secretory mucins and

membrane-bound (transmembrane) mucins. Secretory mucins form a protective layer over organs and create a biochemical barrier against pathogens while membrane-bound (transmembrane) mucins are retained in the plasma membrane due to the presence of a transmembrane domain, which plays a role in transmitting signals [62]. Mucin 2 was the first gel-forming mucin to be discovered in humans. Thinner and discontinuous mucus and decreased expression of MUC2 mucin have been reported in UC patients and in DSS-induced colitis mice models [62–64]. Suppressed MUC2 mucin levels may be attributed to altered translation or altered post-translational levels, independent of MUC2 mucin transcription rates [65]. LncRNAs are important gene expression regulators by targeting miRNA to influence mRNAs stability of encoding genes. For instance, lncRNA DANCR was up-regulated while miR-125b-5p, MUC2, zonula occludens 1 (ZO-1) and Claudin-2 expression levels were suppressed in DSS-induced UC mice models. Silencing DANCR inhibited inflammatory factor expression, up-regulated MUC2, ZO-1 as well as claudin-1 protein levels and suppressed cell apoptosis, thereby attenuating DSS-induced endothelial injury. Notably, these effects could be counteracted by miR-125b-5p inhibitor [66], suggesting that miR-125b-5p increased the translation of targets by both transcriptional and post-transcriptional mechanisms, rather than repressive function.

The epithelial cells located beneath the mucus layer are the integral components of the protective epithelial barrier against bacterial invasion and play an important role in maintaining intestinal homeostasis. The complete epithelial barrier limits interactions between the host immune responses and intestinal microbiota [67]. The thinning of the mucus layer caused by various factors increases the direct interaction between bacteria and the epithelial cells [68]. Dysregulated intestinal epithelial barriers mean a decline of intestinal defense and thus an increased chance of colitis occurrence and development.

The intestinal epithelial barrier defense system consists of a protein complex between adjacent cells, including tight junctions (TJ), adherent junctions (AJ) and desmosomes [69]. As a network of transmembrane proteins, TJ proteins control paracellular permeability [70]. Increased permeability was observed in UC, in tandem with TJ structural abnormality and down-regulation and redistribution of TJ or AJ proteins [71–73]. LncRNAs are involved in regulating the structure and functions of TJ, including the endocytosis of junction proteins, reduced TJ protein expressions and activating the myosin light-chain kinase (MLCK) to promote cytoskeletal contractions. The lncRNA CCAT1 expression level is increased in UC patients and acted as a sponge for miR-185–3p, by binding the 3′ untranslated region (UTR) of MLCK mRNA to inhibit its expression. The MLCK plays a crucial role in myosin light chain (MLC) phosphorylation and the subsequent TJ proteins distribution, leading to increased paracellular permeability [74]. LncRNA H19 was found to be up-regulated in UC patients. It serves as a precursor for miR-675 and increases the cellular abundance of miR-675, which targets the 3' UTR sequence of vitamin D receptor (VDR) mRNAs to suppress ZO-1 and E-cadherin expressions, resulting in epithelial barrier defects [76]. The RNA-binding protein (HuR) prevents the stimulation of miR-675 caused by overexpression of H19, promotes ZO-1 and E-cadherin expressions, and restores epithelial barrier functions [76]. LncRNA PlncRNA1 acts as a sponge for miR-34c, negatively regulating the expression of miR-34c. Overexpressed lncRNA PlncRNA1 down-regulates miR-34c to target Myc-associated zinc finger protein (MAZ) and up-regulates its expression. Physiologically, MAZ can bind promoter regions of ZO-1 and occludin and its up-regulation promotes ZO-1 and occluding expressions, thereby protecting intestinal epithelial barrier functions [77]. Elevated lncRNA NEAT1 expression increases colon tissue permeability and suppresses the expressions of junction complexes (ZO-1, claudin-5 and occludin). The knockdown of NEAT1 reduced colon tissue permeability and increased the expression of junction complexes, maintaining intestinal barrier integrity [78]. Compared to controls, downregulated lncRNA CKDN2B-AS1 expression were noted in active UC patients, resulting in increased colonic barrier damage. Claudin-2, as the major molecule that regulates the barrier, was almost entirely absent in CDKN2B-AS1 down-regulated cells. Mechanistically, CKDN2B-AS1 down-regulation increased colonic barrier damage by suppressing claudin-2 expression [79]. LncRNA MALAT1 was significantly down-regulated in intestinal mucosa of CD patients and in colitis mice models. MALAT1 knockout mice were highly susceptible to DSS-induced colitis. MALAT1 promoted intestinal barrier functions and intestinal homeostasis by sponging miR-146b-5p, which targeting increased the expressions of apical junction complex (AJC) proteins (NUMB and CLDN11). Therefore, the MALAT1-miR-146b-5p-NUMB/CLDN11 pathway has a vital role in maintaining intestinal barrier integrity and intestinal homeostasis [80]. These findings show that various lncRNAs are involved in IBD processes.

In summary, in the regulation of the intestinal mucosal barrier, lncRNAs exhibit diverse mechanisms of action. They can directly target the downstream gene mRNAs, thereby influencing processes such as splicing, editing, subcellular distribution and stability. Additionally, lncRNAs can establish competing endogenous RNA (ceRNA) networks with mRNAs by sharing miRNA response elements. Furthermore, lncRNAs may serve as miRNA precursors and provide a scaffold for RBPs and miRNAs, thereby controlling the expression of mucin and tight junction proteins. These intricate processes collectively contribute to the maintenance of biochemical and physical barriers in the intestines, crucial for preserving intestinal homeostatic status (Fig. 4).

LncRNAs regulate epithelial cell proliferation and apoptosis

Inflammatory cytokines from various mucosal immune cells, in addition to controlling multiple aspects of the immune response, can also disturb the balance between intestinal epithelial cell (IEC) proliferation and apoptosis in inflammatory intestines [81]. The IECs function as physical barriers between the lumina and the external environment to affect host defenses, mucosal homeostasis, and immune responses [82]. Epithelial cell apoptosis increases with the progression of IBD and excess apoptosis of IECs destroys epithelial barrier integrity, thereby promoting microbial invasion and antigen uptake, and enhancing inflammatory responses [83]. Therefore, during IBD pathogenesis, epithelial remodeling often occurs simultaneously with immune responses. LncRNAs affect cell proliferation, differentiation, apoptosis, and migration via a series of signaling pathways or regulatory networks (Fig. 5).

NF-κB pathway

LncRNA ANRIL is up-regulated in colonic mucosa tissues of UC patients. Suppression of ANRIL negatively regulated the expression of miR-323b-5p, which in turn down-regulated its downstream target, TLR4. The inhibiting effects of ANRIL on cell apoptosis and pro-inflammatory cytokines production may also be achieved by downregulating the miR-323b-5p/TLR4/MyD88/NF-κB pathway, thus inhibiting the development of UC [84]. Higher levels of lncRNA NORAD were observed in colonic mucosal

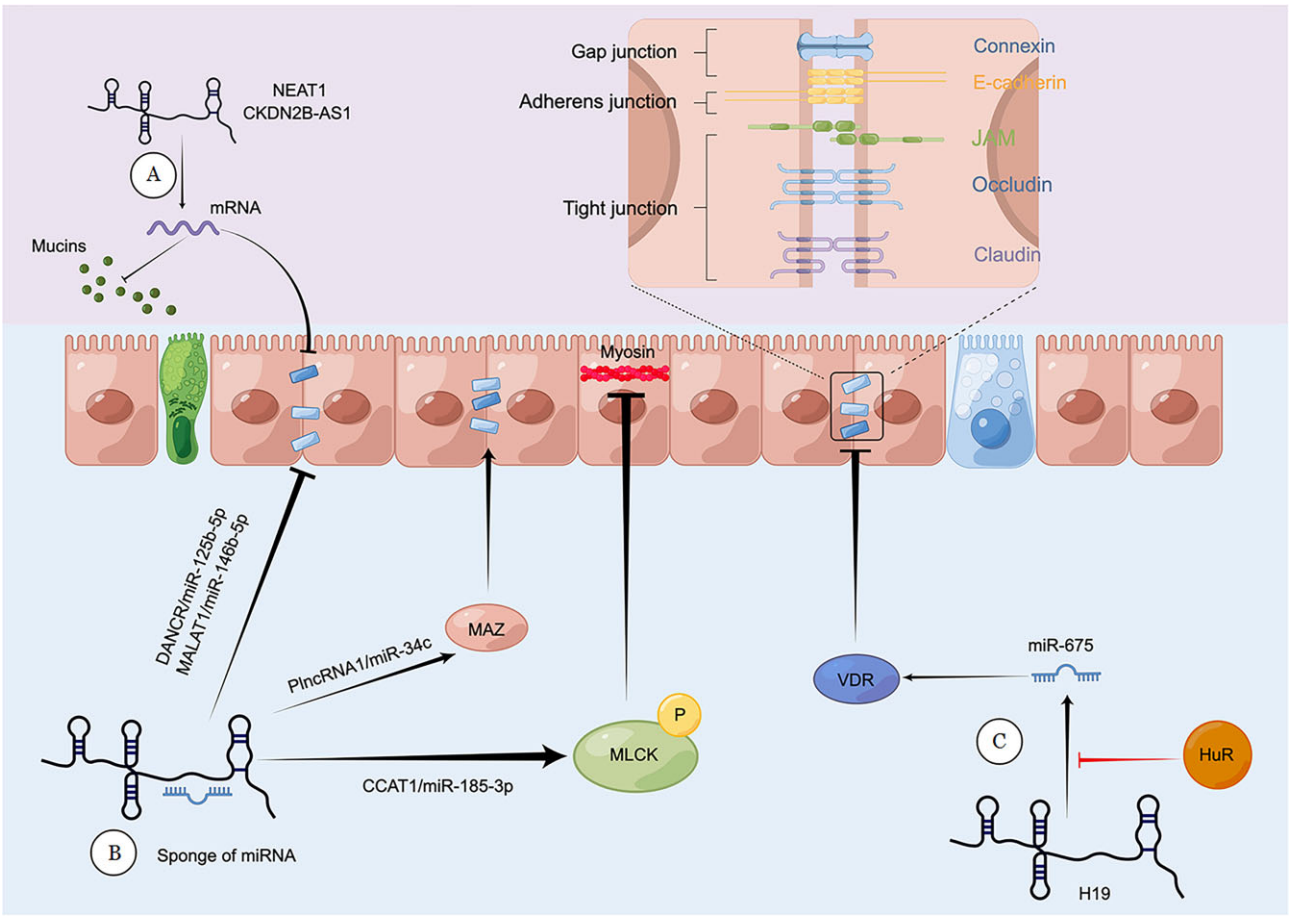

Figure 4. LncRNAs regulate mucosal biochemical and physical barriers. (A) LncRNAs directly target mRNA and regulate their splicing, editing, subcellular distribution and stability. (B) LncRNAs and mRNAs can form competing endogenous RNA (ceRNA) networks in which crosstalks occur through shared miRNA response elements. (C) LncRNAs act as precursors of miRNA and scaffolds of RBPs and miRNAs.

tissues of UC patients [85]. NORAD inhibition impaired TNF-α-induced cell apoptosis and inflammation by modulating the NF-κB signaling via the miR-552–3p/MYD88 axis. LncRNA 78583 and HOXB13 were significantly down-regulated and miR-3202 was up-regulated in UC patients. Lnc78583 up-regulated HOXB13 and IL-10, down-regulated phosphorylated NF-κB (p-NF-κB) and inhibited miR-3202 expression, suggesting that it plays a protective role against intestinal inflammation by targeting miR-3202/HOXB13 [86]. In addition, lncRNAs could directly target mRNAs to regulate gene expression. LncRNA NEAT1 can directly bind to the 3'UTR of the TNFRSF1B mRNA and activated inflammatory response via up-regulating TNFRSF1B, which is a receptor of TNF-α. TNFRSF1B activated its downstream molecule, NF-κB p65, which was then translocated from the cytoplasm to the cell nucleus, initiating the inflammatory cascade by recruiting IL1R1, a pro-inflammatory effector [87]. Bioinformatics analysis showed that LncRNA IFNG-AS1 was significantly up-regulated in UC patients, and IFNG-AS1, which is located adjacent to the *IFNG* gene, was associated with SNP rs7134599, a susceptible locus to UC. Thus, IFNG-AS1 enhances inflammatory responses via recruiting NF-κB and up-regulating downstream inflammatory mediators, such as TNF-α, IFNG and IL-1β, aggravating intestinal inflammation [88, 89]. In inflamed mucosa of UC patients, down-regulation of the lncRNA GAS5 increased the expression of MMP2 and MMP9, which are important mediators of inflammatory response. One potential mechanism by which overexpression of GAS5 suppresses the transcription of MMP2 and MMP9 is by recruiting the histone methyltransferase polycomb repressive complex 2 to the promoter region of these target genes, thereby inmeding their expression. Meanwhile, GAS5 alleviated LPS-induced inflammatory damage through up-regulating Krüppel-like factor 2 and inhibiting the NF-κB pathway, exerting strong anti-inflammatory effects [90]. High expression level of lncRNA PINT was observed in intestinal mucosal tissues of UC patients [91]. PINT acted as a transcriptional regulator of several NF-κB-dependent cytokines and chemokines, such as TNF-α and ICAM-1, and as a modular scaffold for p65 and EZH2, coordinating their localization and specific binding to the target genes (TNF-α). LncRNA NAIL was up-regulated in UC. NAIL regulated inflammation via inactivating Wip1, which could coactivate p38 and NF-κB, leading to differentiation of precursor cells in bone marrow into immature myeloid cells, recruitment of macrophages to the site of inflammation and expression of inflammatory genes in colitis [92].

PI3K/Akt pathway

LncRNA MALAT1 and lncRNA ANRIL were up-regulated in colonic mucosa tissues and plasma of UC patients. In addition, a significant positive correlation was found between the expression levels of the two lncRNAs in UC patients. LncRNA MALAT1 overexpression up-regulated lncRNA ANRIL, which promoted apoptosis of fetal human cells (FHCs). Previous research reported that both lncRNA MALAT1 and lncRNA ANRIL had cross talk with the

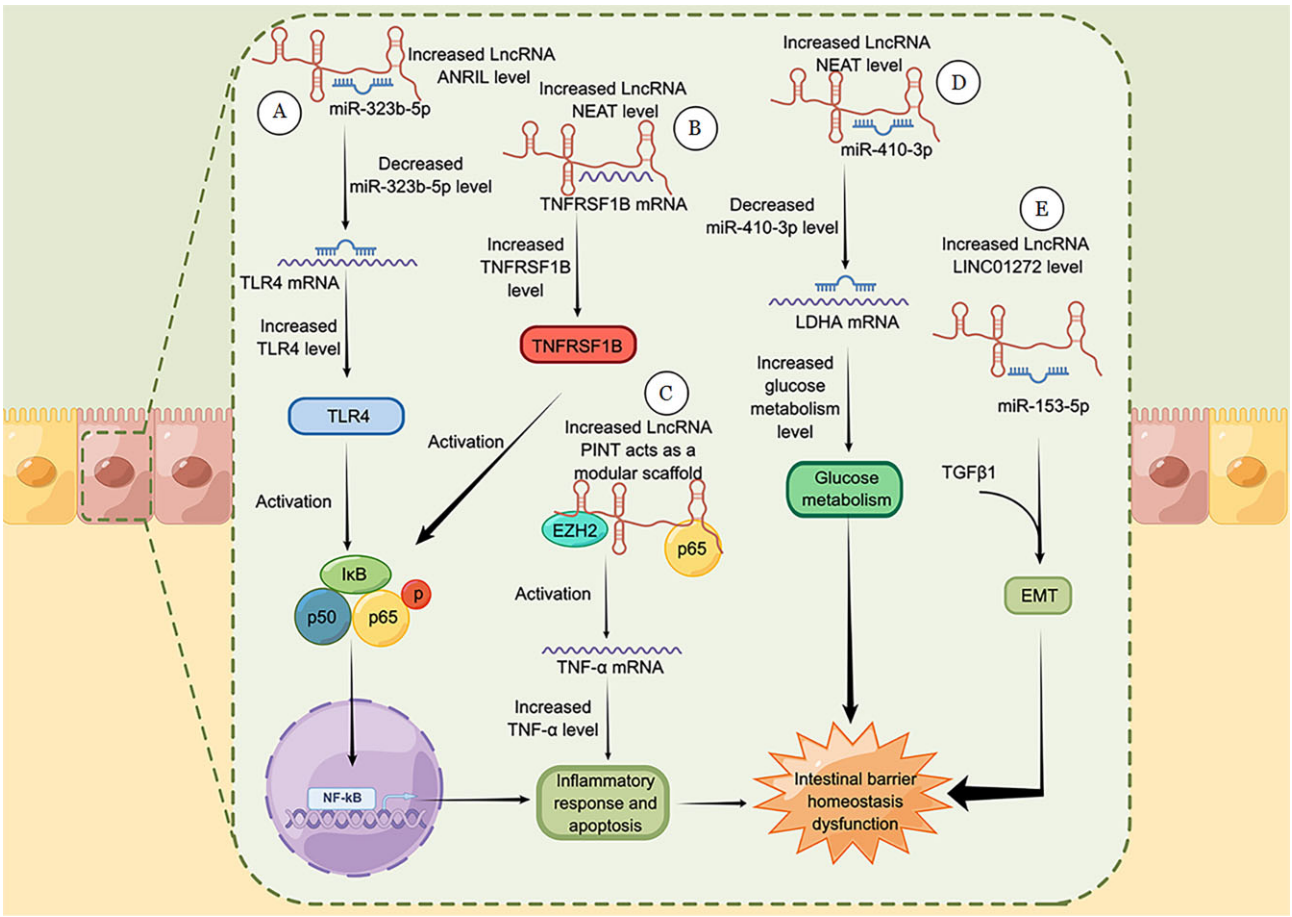

Figure 5. LncRNAs regulate epithelial cell proliferation and apoptosis. (A) LncRNAs regulate the expression of downstream target genes through sponge miRNA, and then activate the NF-κB pathway, promoting inflammation and apoptosis. (B) LncRNAs directly target mRNAs to regulate gene expression, activating the NF-κB pathway and promoting inflammation and apoptosis. (C) LncRNAs act as modular scaffolds for RNA binding proteins, coordinating their localization and specific binding to the target genes, inducing cell apoptosis and inflammation. (D) LncRNA NEAT1 regulates glucose metabolism via miR-410–3p/LDHA axis, influencing intestinal barrier homeostasis. (E) LncRNA LINC01272 promotes TGF-β1-induced epithelial-mesenchymal transition (EMT) by targeting miR-153–5p, leading to loss of epithelial cells and increase in tissue damage.

PI3K-AKT pathway [93], leading to the speculation that the PI3K-Akt pathway contributes in the pathogenesis of UC by mediating the interaction between MALAT1 and ANRIL. LncRNA NEAT1 was up-regulated in the colon tissue of UC patients. MiR-603 was down-regulated in NEAT1-knockdown, which increased cell viability and decreased cell apoptosis and production of cytokines. Fibroblast growth factor 9 (FGF9) was a potential target of miR-603 and negatively regulated by miR-603 [94]. FGF9 affected several biological processes, including inhibition of apoptosis and regulation of inflammatory response via the PI3K/Akt signaling pathway [95, 96]. In addition, NEAT1 regulated the release of cytokines as well as cell survival, apoptosis, proliferation, and differentiation via the miRNA-204–5p/PI3K-Akt3 axis in DSS-induced mice [97].

MAPK pathway

LncRNA Mirt2 levels were significantly lower in the plasma of UC patients. Mirt2 silencing led to increased apoptotic rates of HCnEpCs, which contributed to the development of UC. Elevated levels of Mirt2 may lead to the deactivation of MAPK pathway, which decreased the production of pro-inflammatory cytokines and increased the production of the anti-inflammatory IL-22, suggesting its potential as a treatment for UC [98].

LncRNA/miRNA regulatory networks

LncRNA ANRIL expression was negatively correlated with the risk of IBD, inflammation, and active disease status in IBD [99]. Its over-expression might inhibit the production of inflammatory cytokines production, prevent cell apoptosis and maintain barrier function, suggesting its potential as a therapeutic target in UC. ANRIL interacts with various miRNAs, including miR-195–5p and miR-16–5p, to modulate inflammation response, cell proliferation and apoptosis [100]. The glucose metabolism in the IECs of UC patients was remarkably higher when compared to that in normal controls. The increased glucose metabolism was facilitated by LncRNA NEAT1 and inhibited by miR-410–3p, leading to aggravation of LPS-induced dysfunction in the IECs. Lactate dehydrogenase A (LDHA), a key enzyme in glucose metabolism, was directly targeted by miR-410–3p. Inhibiting NEAT1 maintained the homeostasis of the glucose metabolism, thereby alleviating dysfunction in the IECs [101]. This effect is thought to be mediated via the miR-410–3p-/LDHA axis. LncRNA TUG1 was down-regulated in colonic mucosa tissue of UC patients and in TNF-α-treated HT-29 cells [102]. Forced over-expression of TUG1 can inhibit miR-142–5p and up-regulate SOCS1 expression. High expression of SOCS1, which belongs to the suppressors of cytokine signaling (SOCS) family, led to suppression of pro-inflammatory cytokines production and

promoted cell viability [103]. Thus, the TUG1/miR-142–5p/SOCS1 axis is considered a crucial pathway that modulates immune responses in UC. TUG1 could also serve as a central platform for homeostasis by binding distinct effector molecules. Binding of TUG1 to HuR positively regulated the HuR/c-myc axis, resulting in HuR up-regulation and subsequently c-myc up-regulation, promoting IECs proliferation and mucosal growth. In contrast, binding of TUG1 to miR-29b-3p negatively regulated the miR-29b-3p/CDK2 axis, eventually leading to CDK2 restoration, inhibiting intestinal mucosal growth. This implies that TUG1 maintained intestinal epithelial homeostasis by regulating the balance between the HuR/c-myc signaling and the miR-29b-3p/CDK2 signaling pathways [104]. LncRNA MEG3 and IL-10 levels were significantly decreased whereas miR-98–5p was up-regulated in UC models. MEG3 over-expression alleviated inflammatory response, apoptosis, and pyroptosis by up-regulating IL-10 via sponging miR-98–5p [105]. MEG3 could also competitively binds to miR-20b-5p to promote CREB1 transcription [25]. Inhibition of CREB1, a transcription factor belonging to the basic leucine zipper family, eliminated its anti-inflammatory effect in UC [106, 107]. LncRNA SNHG5 was up-regulated in intestinal mucosa tissues of UC patients. Down-regulation of SNHG5 can up-regulate miR-375 and down-regulate JAK2, thereby promoting cell proliferation and inhibiting cell apoptosis [108]. Similarly, forced over-expression of lncRNA H19 increased cell proliferation and epithelial regeneration and decreased the levels of inflammatory cytokines by targeting the miR-141/ICAM-1, miR-139/CXCR4 and miR-331–3p/TRAF4 axis [109, 110]. Up-regulation of lncRNA CRNDE promoted colonic epithelial cell apoptosis via the miR-495/SOCS1 axis [111]. LncRNA KIF9-AS1 silencing attenuated the colonic cell apoptosis and alleviated colon inflammation-induced intestinal injury by regulating the miR-148a-3p/SOCS3 axis [112]. Up-regulation of lncRNA LINC01272 in tissue and plasma samples of CD patients promoted TGF-β1-induced epithelial-mesenchymal transition (EMT) by targeting miR-153–5p, leading to loss of epithelial cells and increase in tissue damage [113]. In colon tissues of CD patients, there was a notable rise in the expression of LncRNA CNN3-206. The increased expression led to up-regulation of Caspase 10 by absorbing miR-212, consequently enhancing apoptosis, migration and invasion of IECs [114].

Other regulatory networks

It has been reported that lncRNA PMS2L2 was down-regulated in the plasma of UC patients. LncRNA PMS2L2 over-expression in human colonic epithelial cells (HCnEpCs) suppressed LPS-induced cell apoptosis by inhibiting miR-24 expression via promoting the methylation of *miR-24* gene [115]. Overexpression of LncRNA BC012900 in active UC resulted in the increased expression of PPM1A (protein phosphatase), activating the expression of the tumor suppressor gene *TP53*/*p53*, which led to G2/M cell cycle arrest and apoptosis [116]. LncRNA Gm31629 deficiency exacerbated intestinal inflammation and delayed epithelial regeneration. Conversely, its over-expression promoted cell proliferation, facilitated epithelial regeneration and protected the intestinal mucosa against inflammation damage. Mechanically, Gm31629 binds to YB-1 protein and prevents its degradation, thus, promoting the expression of E2F target genes CCND1 [117]. This indicated that lncRNAs can bind to specific enhancers (nucleic acids and proteins) to exert synergistic effects.

In summary, the above findings demonstrate that lncRNAs regulate the occurrence and development of IBD through diverse mechanisms: (1) lncRNA directly targets and regulates mRNA splicing, editing, subcellular distribution and stability; (2) lncRNAs and mRNAs can form competing endogenous RNA (ceRNA) networks with crosstalk between them through shared miRNA response elements; (3) lncRNAs act as the precursor of small lncRNA and the scaffold of RBP and miRNA; (4) lncRNAs interact with proteins to regulate downstream pathways; (5) lncRNAs interact with miRNA and participates in epigenetic regulation; (6) lncRNAs bind to transcriptional regulators to regulate related molecular signaling pathways, such as macrophage polarization.

LncRNAs regulate immune responses

Disruptions in the composition or function of gut microbiota, along with a thinner mucus layer and compromised epithelial cell barrier, collectively contribute to the activation of the host immune response. This immune response is mediated, in part, by various immune cells such as dendritic cells, macrophages, neutrophils, T cells, and innate lymphoid cells, along with the presence of inflammatory cytokines. These immune factors play a pivotal role in initiating and advancing IBD progression. The imbalance between pro-inflammatory and anti-inflammatory cytokines in IBD prevents the resolution of inflammation and instead leads to disease progression and tissue destruction [118]. Elevated pro-inflammatory cytokine levels contribute to a pro-inflammatory cascade that promotes epithelial injury, intestinal barrier defects, and tissue damage [119]; and yet, anti-inflammatory cytokines, as an important part of cytokine networks, can also be used for treatment of chronic intestinal inflammation. LncRNAs, acting as biological regulatory molecules, demonstrate distinct expression within various cells, tissues, and organs. This allows them to play a role in host immune responses (Fig. 6).

Innate immune responses

Innate immunity is the first line of defense against pathogens. Innate immune cells, such as dendritic cells (DCs), macrophages, neutrophils and innate lymphoid cells can sense the changes in intestinal homeostasis and respond to pathogen associated molecular patterns (PAMPs). Defective innate immune responses can lead to IBD.

Dendritic cells (DCs) play a critical part in induction of IBD immune pathogenesis by sensing environmental changes and transmitting signals [120]. Changes in microbiota, decreased mucus layer and increased permeability of epithelial barriers in IBD enhances the entry of antigens into the lamina propria to activate DCs. The PAMPs are recognized by Toll-like receptors of DCs, resulting in inflammation by secreting pro-inflammatory cytokines and chemokines to recruit neutrophils, as well as translating innate to adaptive immune responses. LncRNA MALAT1 over-expression promotes dendritic cell-specific intercellular adhesion molecule-3 grabbing nonintegrin (DC-SIGN) expression by acting as a molecular sponge for miR-155, favoring the transition of DCs to tolerant phenotypes [121]. In DSS-induced colitis mice models, melatonin promoted bone marrow derived dendritic cell (BMDCs) transformation into immune tolerant phenotypes by affecting lncRNA ENSMUST00000226323. From a molecular interaction perspective, lncRNA ENSMUST00000226323 interacted with miRNA-709. *Ywhaz* and *Ccl9*, two pivotal genes in the PI3K-Akt pathway, were predicted to be the targets of miRNA-709. ENSMUST00000226323, Ywhaz and Ccl9 might play regulatory roles in the PI3K-Akt pathway through miRNA-709 and participate in functional changes of BMDCs in colitis (Fig. 6A) [122]. Therefore, lncRNAs regulate IBD by altering BMDCs functions.

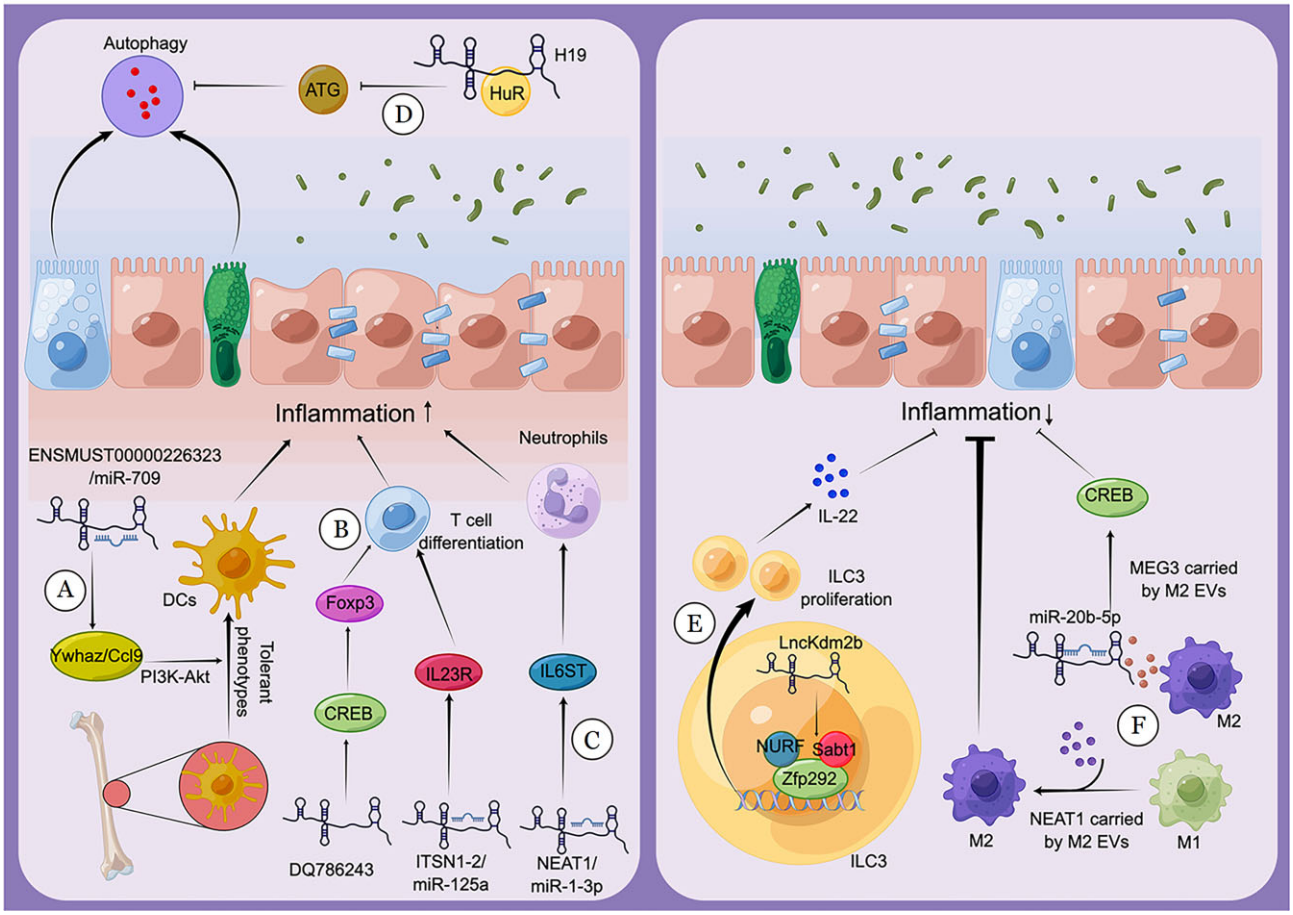

Figure 6. LncRNAs regulate immune responses and epithelial restitution. (A) LncRNAs affect the transformation of BMDCs into immune tolerant phenotypes. (B) LncRNA regulate Th cell differentiation to balance the production of inflammatory cytokines. (C) LncRNAs are involved in neutrophil infiltration to promote IBD occurrence and development. (D) LncRNAs participate in regulation of autophagy to regulate intestinal homeostasis. (E) LncRNAs promote cell proliferation to sustain the maintenance and functions of ILC3s. (F) LncRNAs participate in exosome-mediated polarization of macrophages.

Macrophages are abundant in the lamina propria of intestinal mucosa to maintain intestinal homeostasis. In IBD, the macrophage phenotype shifts to M1 during inflammatory progression, which secretes pro-inflammatory cytokines, whereas during disease remission, the macrophage phenotype shifts to M2, which secretes anti-inflammatory cytokines. LncNEAT1 plays a role in inflammatory responses by regulating intestinal epithelial barrier and through exosome-mediated macrophage polarization. Inhibition of NEAT1 suppresses inflammatory responses by promoting macrophage M1 transformation to M2, thereby improving intestinal epithelial barrier permeability [78]. Due to the anti-inflammatory activities of M2 macrophages, M2-macrophage-derived extracellular vesicles (M2-EVs) have become key mediators in many inflammatory disease processes [123]. The M2-EVs play anti-inflammatory roles via surface-bound chemokine receptors and anti-inflammatory cytokines released by M2 macrophages. LncRNA MEG3 can be delivered by EVs to regulate IBD procession [25]. M2-EVs suppress inflammatory responses by up-regulating lncRNA MEG3, which competitively bind miR-20b-5p to promote cAMP response element binding protein 1 (CREB1) transcription, thereby reducing inflammatory responses in UC. The results indicate that M2-EVs can be utilized to treat UC and other diseases (Fig. 6F).

Neutrophils play a major role in UC mucosal inflammation and injury by secreting toxic mediators, including neutrophil elastase, myeloperoxidase, reactive oxygen species and proinflammatory cytokines [124]. Based on biological functions of non-coding RNAs involved in UC recurrence and progression, Lu et al. constructed competing endogenous RNA (ceRNA) networks of lncRNAs, microRNAs and mRNA. They found that 4 lncRNAs, 5 miRNAs, and 52 mRNAs are involved in interleukin family signals, neutrophil degranulation, adaptive immunity, and cell adhesion pathways [125]. Correlation analyses showed that ceRNA networks are highly associated with most of the UC-associated infiltrating immune cells, particularly neutrophils, macrophages and T cells. LncRNA MIR4435-2HG acts as a miRNA sponge for TGF-β1 and activated TGF-β signaling, suggesting that MIR4435-2HG is a crucial mediator of inflammatory processes. Yin et al. discovered and validated a novel ceRNA immunoregulatory axis in ulcerative colitis-associated colorectal cancer (CAC) progression [126]. LncRNA NEAT1 functions as ceRNA to sponge miR-1–3p and promote IL6ST expression. Neutrophils were the central immune cells in CAC development, and IL6ST expression was positively correlated with neutrophil counts. Upregulated IL6ST affected the NF-κB pathway and neutrophil infiltration, and promoted CAC development (Fig. 6C).

As components of the innate immune system, innate lymphoid cells (ILC) reside in mucosal surfaces to promote immune responses, maintain mucosal integrity and facilitate lymphoid organogenesis [127]. Intestinal group 3 ILCs (ILC3s) are enriched in

intestinal lamina propria [128] and lncKdm2b is highly expressed in ILC3s [129]. LncKdm2b expression recruits the chromatin organizer (Satb1) and the nuclear remodeling factor (NURF) complex onto the Zfp292 promoter region to initiate its transcription, thereby promoting their proliferation to sustain the maintenance of ILC3s. Deregulated ILC3 functions can lead to colitis occurrence and development [130]. Therefore, we postulate that lncKdm2b participates in the development of colitis (Fig. 6E).

Autophagy is an evolutionarily conserved process in eukaryotes through which damaged proteins and organelles are degraded inside the lysosomes [131]. Autophagy plays a vital role in maintaining intestinal homeostasis and functions, regulating gut microbiota composition and altering host immune responses [132]. The lncRNAs interact with autophagy to regulate intestinal homeostasis. LncRNA H19 participates in the regulation of autophagy and in functions of paneth and goblet cells in the intestinal epithelium [133]. Intestinal mucosal tissue samples from patients with sepsis and septic mice models exhibited increased levels of H19, resulting in autophagy inactivation, defects of paneth and goblet cells and disruption of epithelial barrier functions. Deregulated expressions of autophagy associated genes, such as *Atg16L1*, *Atg5*, and *Atg7* have also been reported in IBD patients [134]. The exact mechanisms by which H19 deletion activates intestinal epithelial autophagy have not been determined. Mechanistically, HuR (an RNA binding protein RBP that can bind H19) regulates autophagy by altering ATG expression [135]. Suppressed HuR levels in the intestinal mucosa of IBD patients were accompanied by specific suppression of ATG16L1 level. HuR directly bound mRNAs encoding ATG5/12/16 via 3-UTRs, enhanced their stability and translation, and increased cellular abundances of ATG proteins (Fig. 6D) [136]. Therefore, we postulate that under IBD conditions, H19 competitively binds HuR, thereby inhibits autophagy by suppressing ATGs expressions and repressing paneth and goblet cell functions. This leads to disruption of the intestinal epithelial defense and aggravates mucosal injury as well as inflammation. In future, studies should be performed to confirm this phenomenon and to elucidate on the underlying mechanisms.

Adaptive immunity

Adaptive immunity functions in tandem with innate immunity to produce effective immune responses against invading pathogens. T lymphocytes are vital players in adaptive immune responses. Original T cells are activated and are differentiated into different subsets, such as Th1, Th2, Th17 and Treg cells. In IBD, T cell response disorders and imbalanced T cell subsets lead to disturbances in cytokine release, which disrupts gut homeostasis. Pathologically, CD manifests with Th1 and Th17 immune responses, while UC is considered to be Th2-mediated disease [137, 138]. Dysregulated lncRNAs regulate the activities and differentiation of T cells and further affects the balance between pro-inflammatory and anti-inflammatory cytokines (Fig. 6B) [139]. LncRNA ITSN1-2 was up-regulated in UC patients and was closely associated with high risks and activities of IBD. ITSN1-2 acts as a ceRNA of IL-23R, and its up-regulation promotes the activation and proliferation of $CD4^+$ T cells as well as the differentiation of Th1/Th17 cells by sponging miR-125a [140]. LncRNA IFNG-AS1 is positively correlated with UC severity. Over-expressed IFNG-AS1 activate primary T cells, leading to up-regulation of Th1 pro-inflammatory cytokines (IFNG and IL2), and down-regulation of Th2 anti-inflammatory cytokines (IL10 and IL13) [141]. The IFNG-AS1-induced cytokine switching might involve T-bet, which regulates T cell differentiation and IFNG-AS1 expression [142]. LncRNA DQ786243 levels were significantly elevated in active CD patients, relative to healthy controls and inactive CD patients [143]. DQ786243 up-regulated CREB expression and phosphorylation levels, which is critical for activities of the TCR response element in forkhead box P3 (Foxp3), a master transcription factor that regulates Tregs functions and development [144, 145]. These findings imply that DQ786243 influences IBD processes by affecting the expressions of CREB and Foxp3 via regulating Treg functions. By analyzing the transcriptome of $CD4^+$ T cells in the terminal ileum propria of CD patients, a novel lincRNA XLOC_000 261 was identified to be a negative regulator of RORγt (a Th17-defining transcription factor) and impacts the pro-inflammatory capacity of Th17 cells, which affects adaptive immune responses in CD [139]. Li et al. analyzed the expression profiles of long noncoding RNAs in intestinal mucosa of CD patients and found that lncRNA ENST00000487539.1_1 promotes Th17 cell differentiation by regulating related target genes, such as IL17, RORγ-t, TGF-β, MHC-II, IL-22 [146]. Further studies are needed to investigate the biological functions and underlying mechanisms of ENST0000487539_1.1.

LncRNAs as diagnostic biomarkers for IBD

The expression profile of lncRNA in colonic biopsy and plasma samples is significantly different between IBD patients and healthy controls [116, 148–151]. This indicates that lncRNAs hold potential as valuable diagnostic markers for IBD (Table 2). Wu et al. identified 329 and 126 lncRNAs, which were up-regulated and down-regulated in active UC tissues, respectively, compared with normal control tissues [116]. Li et al. reported that lncRNA Mirt2 and lncRNA IFNG-AS1 were negatively correlated, with Mirt2 being down-regulated and IFNG-AS1 being up-regulated in UC patients' plasma compared with healthy control. Receiver operating characteristic (ROC) curve showed that the area under the curve (AUC) was 0.86 for plasma Mirt2 (0.92 in another study) and 0.84 for plasma IFNG-AS1 [98, 152]. This suggested the promising diagnostic values of these two lncRNAs for UC. IL-22, known for its anti-inflammatory properties, play a crucial role in inhibiting intestinal inflammation. Of particular interest is the positive correlation observed between IL-22 and Mirt2 in UC patients. Further analysis of the relationship between IL-22/Mirt2 and plasma C-reactive protein (CRP) levels revealed a significant and inverse correlation between the plasma levels of IL-22 and Mirt2 with CRP levels. CRP, an acute phase reaction protein (APRP), is commonly used to assess inflammatory status. Given these findings, a combined assessment of IL-22, Mirt2, and CRP levels in plasma holds promise for aiding in the diagnosis and prognosis assessment of UC. The lncRNA MALAT1 level was markedly higher in colon tissues of UC patients compared with healthy controls, with AUC of 0.94, indicating that lncRNA MALAT1 could efficiently distinguish UC patients from health controls [94]. Wang et al. reported that lncRNA KIF9-AS1, LINC01272 and DIO3OS might be potential diagnostic biomarkers for IBD [153]. In this study, compared with healthy controls, KIF9-AS1 and LINC01272 were significantly up-regulated whereas DIO3OS were down-regulated in tissue and plasma samples from UC patients and CD patients. The AUC of KIF9-AS1, LINC01272 and DIO3OS expression was 0.872, 0.777 and 0.653 between UC patients and healthy controls and 0.811, 0.887 and 0.794 between CD patients and healthy controls, respectively. LncRNA ANRIL levels were lower in UC patients and CD patients compared with the controls. ROC curve analyses showed that lncRNA ANRIL could distinguish UC patients and CD patients from controls with an AUC of 0.789 and 0.771, respectively [99]. In addition, lncRNA ANRIL expression was lower in both

Table 2. Diagnostic values of lncRNAs as biomarkers for UC and CD.

LncRNAs	Sample	Compared groups	Statistical indicators				Reference
			Sensitivity (%)	Specificity (%)	AUC	*P* value	
Up-regulated in UC							
ITSN1-2	colonic tissue	active UC vs. healthy controls	–	–	0.857	–	[140]
		remission UC vs. healthy controls	–	–	0.678	–	
		active UC vs. remission UC	–	–	0.754	–	
	PBMCs	active UC vs. healthy controls	–	–	0.828	–	
		remission of UC vs. healthy controls	–	–	0.741	–	
		active UC vs. remission UC	–	–	0.649	–	
MALAT1	plasma	UC vs. healthy controls	–	–	0.94	–	[93]
IFNG-AS1	plasma	UC vs. healthy controls	–	–	0.84	<0.05	[152]
LINC01272	plasma	UC vs. healthy controls	–	–	0.777	<0.0001	[152]
KIF9-AS1	plasma	UC vs. healthy controls	–	–	0.872	<0.0001	[153]
LINC00657	serum	UC vs. healthy controls	92.3	100	0.923	<0.0001	[155]
Down-regulated in UC							
CDKN2B-AS1	serum	UC vs. healthy controls	0.822	0.968	0.894	–	[84]
		active UC vs. remission UC	0.733	0.624	0.714	–	
		mild UC vs. moderate UC	0.494	0.730	0.609	–	
		mild UC vs. severe UC	0.494	0.800	0.667	–	
		moderate UC vs. severe UC	0.667	0.511	0.562	–	
ANRIL	PBMCs	UC vs. healthy controls	–	–	0.789	–	[98]
Mirt2	plasma	UC vs. healthy controls	–	–	0.92	<0.05	[102]
Mirt2	plasma	UC vs. healthy controls	–	–	0.86	<0.05	[152]
DIO3OS	plasma	UC vs. healthy controls	–	–	0.653	0.001	[153]
Up-regulated in CD							
LINC01272	plasma	UC vs. healthy controls	–	–	0.887	<0.0001	[152]
KIF9-AS1	plasma	UC vs. healthy controls	–	–	0.811	<0.0001	[153]
Down-regulated in CD							
DIO3OS	plasma	CD vs. healthy controls	–	–	0.794	<0.0001	[153]
ANRIL		CD vs. Health control	86.1	64.2	0.803		[154]
		Active CD vs. healthy controls	85.7	83.6	0.903		
		Remission CD vs. healthy controls	93.2	50.7	0.732		
		Active CD vs. Remission CD	85.7	71.2	0.839	–	

Testing method: RT-qPCR

active CD patients and remission CD patients in comparison with healthy controls. ROC curves revealed that ANRIL expression had an AUC of 0.803, which could distinguish patients with CD from the controls with 86.1% sensitivity and 64.2% specificity. ANRIL also showed good values in differentiating active CD patients from controls with AUC of 0.903, sensitivity of 85.7% and specificity of 83.6%, remission CD patients from controls with AUC of 0.732, 93.2% sensitivity and 50.7% specificity and active CD patients from the remission CD patients with AUC of 0.839, 85.7% sensitivity and 71.2% specificity [154]. Correlation analysis showed that ANRIL expression was negatively correlated with ESR, CRP and IL-6 levels in UC and CD patients, suggesting its potential value for IBD management [99, 154]. A study conducted in Egypt reported that serum lncRNA 00657 could efficiently distinguish UC from controls with an AUC of 0.923, 92.3% sensitivity of and 100% specificity [155]. The expression level of intestinal mucosa and peripheral blood mononuclear cells (PBMCs) lncRNA ITSN1-2 was higher in active UC patients and remission UC patients compared with health controls. ROC curves analysis revealed that intestinal mucosa ITSN1-2 showed an excellent predictive value in active UC with a high AUC of 0.857 and UC of remission with AUC value of 0.678 compared with healthy controls. Similarly, PBMCs ITSN1-2 showed an excellent predictive value in active UC with AUC of 0.828 and a moderate predictive value in remission UC with AUC of 0.741 compared with healthy controls. Furthermore, intestinal mucosa and PBMCs lncRNA ITSN1-2 showed an acceptable value in distinguishing active UC patients from remission UC patients with AUC of 0.754 and 0.649, respectively [140]. Similar results were observed in patients with CD. Intestinal mucosa ITSN1-2 was up-regulated in active CD patients compared with healthy controls and ROC curves analysis further disclosed that intestinal mucosal ITSN1-2 presented with an excellent value in predicting active CD risk with AUC 0.873. As for PBMC ITSN1-2, it was found to be up-regulated in active CD and remission CD patients compared with healthy controls. ROC curves analysis further exhibited that PBMC ITSN1-2 illuminated an excellent value in predicting active CD risk with AUC 0.891 and maid value in predicting R-CD risk with AUC 0.716. Moreover, intestinal mucosa and PBMC ITSN1-2 was positively correlated with both CRP and ESR in CD patients. As for UC patients, intestinal mucosa ITSN1-2 was only positively associated with ESR, while it did not correlate with CRP. Furthermore, PBMC ITSN1-2 showed a positive correlation only with CRP, not with the ESR. In summary, ITSN1-2, similar to CRP and ESR, holds promise as a potential biomarker for assessing the disease activity of IBD.

Although the dysregulation of lncRNAs in IBD tissue or plasma samples is a potentially valuable diagnostic biomarker for IBD, the IBD pathological process is complex and not fully elucidated, there is currently no single gold standard test for diagnosing IBD. Therefore, a combination of several lncRNAs might be necessary to provide an accurate diagnosis. A transcriptomic landscape revealed 370 up-regulated lncRNAs and 375 down-regulated lncRNAs in inflamed UC. The best Support Vector Machines (SVM) classifier performance based on the comparison

between differentially expressed lncRNAs identified in the inflamed UC and healthy controls effectively distinguished inflamed UC and CD from the controls with 94.6% and 100% accuracy, 100% and 100% specificity and 86.7% and 100% sensitivity, respectively. The classifier distinguished inflammatory CD from controls (accuracy 100%, sensitivity 100%, sensitivity 100%), inflamed UC from non-inflamed UC (accuracy 91.7%, specificity 88.9%, sensitivity 83.3%), inflamed CD from non-inflamed CD (accuracy 86.4%, specificity 78.3%, sensitivity 95.2%), and inflamed CD from inflamed UC (accuracy 77.8%, specificity 60.0%, sensitivity 90.4%) [114]. LncRNA CDKN2BAS1 was excellent in distinguishing UC patients from healthy controls with an AUC of 0.894. Furthermore, CDKN2BAS1 combined with miR-16–5p and miR-195–5p could strongly improve the diagnostic efficacy for UC, with an AUC of 0.995, which was higher compared with the that of CDKN2B-AS1 and miR-16–5p combined (AUC = 0.978) and CDKN2B-AS1 and miR-195–5p combined (AUC = 0.975). For distinguishing between active and remission UC patients, CDKN2B-AS1, miR-16–5p, and miR-195–5p combined diagnosis had an AUC of 0.817, which was higher than the diagnosis of CDKN2B-AS1 (AUC = 0.714), miR-16–5p (AUC = 0.710) and miR-195–5p (AUC = 0.639) individually. Individual CDKN2BAS1 could distinguish mild-to-moderate UC patients and mild-to-severe UC patients with an AUC of 0.609 and 0.667, respectively. In comparison, combining CDKN2B-AS1 with miR-16–5p and miR-195–5p improved its efficacy in the diagnosis of mild-to-moderate UC (AUC = 0.638), mild-to-severe UC (AUC = 0.720), and moderate-to-severe UC (AUC = 0.610) [100].

Although emerging evidence supports the use of lncRNAs as potential diagnostic biomarkers of IBD, several issues need to be resolved before they can be applied in clinical application, including sensitivity, specificity, wide applicability and stability of expression. Notably, there may be many IBD-related lncRNAs, but specific serum diagnostic markers for the diagnosis of IBD are lacking. Screening out lncRNAs with high sensitivity and specificity and stable expression as molecular markers among a vast pool of lncRNAs with varying expression changes is a challenging endeavor. To ensure the reliability and accuracy of these lncRNAs as novel biomarkers, it is crucial to include an adequate number of patients in the study. Moreover, for validation purposes, it is essential to recruit new patients, a step that is unfortunately lacking in the vast majority of current published studies. In addition, changes in circulating lncRNA levels in IBD patients may be due to the body's general pathophysiological response to the inflamed bowel tissue, rather than due to direct secretions from intestinal mucosa. This may also explain why there is sometimes a lack of consistency between circulating lncRNA levels and intestinal mucosal lncRNA levels [140]. In the case of non-invasive or minimally invasive sampling, it is likely that a pan-circulating biomarker will be utilized in the near future to diagnose IBD (similar to a combined test of multiple markers). Undoubtedly, the growing global interest in lncRNAs and advancements in technology have paved the way for exploring circulating lncRNAs as potential novel blood biomarkers linked to IBD.

LncRNAs as therapeutic targets and agents for IBD

Apart from their potential as diagnostic biomarkers, lncRNAs also hold promise for clinical applications as potential treatments for IBD. A potential strategy in this regard is to target specific lncRNAs for silencing or over-expression to mitigate the effects of IBD and provide therapeutic benefits. For example, vildagliptin, a dipeptidyl peptidase IV (DPP-IV) inhibitor, strongly inhibited the expression of lncRNA IFNG-AS1 and miR-146a, as well as the PI3K/Akt/NF-κB pathway, but activated CREB and nuclear factor erythroid 2-related factor 2 (Nrf2) signaling pathways, resulting in alleviation of oxidative stress, inflammation and cell apoptosis in acetic acid-induced colitis [89]. In a study focused on pediatric patients with UC, researchers examined the correlation between lncRNA GAS5 and the response to glucocorticoid therapy. They found that lncRNA GAS5 was up-regulated in the PBMCs of pediatric IBD patients who showed an unfavorable response to glucocorticoid treatment. This suggests that lncRNA GAS5 holds promise as a novel pharmacogenomic marker, which could be utilized for personalized glucocorticoid therapy in these patients. Moreover, inhibition of GAS5 restored glucocorticoid response in refractory patients [156]. LncRNA OIP5-AS1 and IL-17 were up-regulated whereas miR-26a-5p was down-regulated in UC, with OIP5-AS1 serving as a miR-26a-5p sponge to modulate the Th17 cells and IL-6 expression. Further, vitamin D treatment could decrease OIP5-AS1 level in both $CD4^+$ T cells and Th17 cells differentiation, therefore decreasing IL-6 level via OIP5-AS1/miR-26a-5p/IL-6 axis [147].

On the other hand, an alternative approach involves utilizing lncRNAs as potential therapeutic agents to target relevant pathogenic mechanisms, rather than treating them as therapeutic targets themselves. A noteworthy example of this is the use of aflavin 3-gallate, a natural compound that mimics the function of lncRNA Gm31629. This compound has been shown to enhance the protein levels of YB-1 and CCND1, along with mRNA levels of E2F target genes, in colon tissues. Consequently, this facilitates epithelial regeneration and effectively mitigates colitis induced by DSS [117]. M2-EVs as critical mediators in various inflammatory diseases [123], exerted potent anti-inflammatory effects by regulating surface-bound chemokine receptors and anti-inflammatory cytokines released by M2 macrophages [157]. M2-EVs reduced inflammatory response by up-regulating lncRNA MEG3, which competitively bound to miR-20b-5p to promote CREB1 transcription, thereby enhancing cell viability and reducing inflammation-induced injury in UC. These results suggested that M2-EVs could be a promising therapeutic target of UC [25]. Technically, one approach is to co-package lncRNAs into M2-EVs with biomimetic nanoparticles to form nanoscale drug delivery systems (DDS) for the treatment of IBD. Another approach is to transfect lncRNA directly into M2 with lentivirus and transfer from M2 to target cells via EVs packaging, thereby improving intestinal inflammation. Both approaches have been demonstrated in studies of EV-coated miRNAs for the treatment of IBD [158–160]. Finally, it is worthwhile to mention that herb-partitioned moxibustion (HPM) could also regulate the expression and functions of lncRNAs. Wang et al. found that HPM improved intestinal inflammation of CD by up-regulating the lncRNA LOC102550026/miR-34c-5p/Pck1 axis and adipocytokine, PPAR, AMPK, FoxO, and PI3K-Akt signaling pathways, which reflect a potential molecular mechanism by which HPM improves CD symptoms [148].

In summary, lncRNAs are novel therapeutic targets and agents that have not been fully exploited for IBD treatment. LncRNAs affect the occurrence and development of IBD through various mechanisms, reflecting their clinical prospects as new therapeutic targets and agents for IBD. With the maturation of lncRNAs *in vivo* targeting technologies, such as the antisense oligonucleotide technology that is currently used to treat human diseases, the development of lncRNA-targeted therapeutic regimens is feasible.

Conclusion

Evidence accumulated shows that lncRNAs participate in gene regulation at multiple levels (epigenetic, transcriptional, and post-transcriptional regulation, etc.) to regulate diverse biological and physiopathological contexts by interacting with DNA, RNA and proteins. Moreover, the ability of lncRNAs to code peptides has broadened our understanding of the important role of lncRNAs in the pathogenesis and development of diseases. This review focuses on the regulatory effects of lncRNA on the composition of intestinal flora, the integrity of the intestinal mucous layer, the functionality of the epithelial barrier, and immune response throughout the development and progression of IBD. Moreover, the future application of lncRNA as biomarkers and therapeutic targets/agents in IBD is discussed.

Over the past few decades, researchers have made great advances in uncovering the mechanism of miRNAs in IBD occurrence and development. LncRNAs have been implicated in the development and progression of IBD and been shown with potential of clinical application in the prediction, diagnosis, treatment and monitoring of IBD. However, many critical, difficult issues must be resolved before lncRNAs can be applied in clinical practice. Among them, testing methods (microarray, RNA-sequencing and qRT-PCR) and sample types (plasma, colonic tissues) should be standardized. Whereas microarray and RNA-sequencing have shown hundreds of lncRNA deregulated in IBD patients, the results of different studies show wide variations and inconsistencies. For instance, the appropriate method(s) for validating the function or application of a specific lncRNA remain uncertain and ambiguous in the current scientific literature. In addition, lncRNAs isolated from blood using minimally invasive methods could be used as ideal biomarkers, but whether their diagnostic value can reach the level in colon tissue is unknown. Like with many other research topics, the under-elucidated mechanisms of lncRNAs in IBD limits their applications in clinical practice. In lncRNAs targeted therapy, there are still multiple uncertainty factors, including choosing appropriate targeting methods and drug vectors. Although initial results from animal studies have been promising, these strategies need to be further validated in clinical trials to assess their feasibility, efficacy, and safety. Despite the many significant challenges, considering the recent successes in COVID-19 mRNA vaccines and other cancer drugs development, we strongly believe that lncRNAs are promising in clinical applications, including biomarkers, prognostic indicators and therapeutic candidates/targets.

In conclusion, this review describes valuable knowledge about the potential mechanisms of lncRNA involvement in IBD and summarizes new findings regarding the role of lncRNAs as diagnostic markers and therapeutic targets/agents for IBD. However, further research in related fields is necessary to address the aforementioned challenges and expedite the clinical translation of these findings.

Acknowledgements

This work was supported by the National Natural Science Foundation of China (Grants No. 82270011 and 81960513), the Scientific Research Foundation of the Affiliated Hospital of Xuzhou Medical University (Grant No. 2020KA010), the Priority Academic Program Development of Jiangsu Higher Education Institutions (PAPD), and Postgraduate Research & Practice Innovation Program of Jiangsu Province (Grant No. KYCX22_2815), the Natural Science Foundation of Guizhou Provincial Scientific and Technology Department Grant (Grant No. (2022)626)) and Scientific Research Foundation of Wenzhou Institute, University of Chinese Academy of Sciences.

The authors would like to thank all the reviewers who participated in the review, as well as MJEditor (www.mjeditor.com) for editing the English of this manuscript. We thank Figdraw (www.figdraw.com) for providing us the graphic materials.

Conflict of interest: All authors declared no conflict of interest. In addition, as an Editorial Board Member of *Precision Clinical Medicine*, the corresponding author Min Wu was blinded from reviewing or making decisions on this manuscript.

Author contributions

Fei Jiang drafted the manuscript and prepared figures. Min Wu revised the manuscript. Rongpeng Li conceived the idea and revised the manuscript.

References

1. Khor B, Gardet A, Xavier RJ. Genetics and pathogenesis of inflammatory bowel disease. *Nature* 2011;**474**:307–17. https://doi.org/10.1038/nature10209.
2. Kobayashi T, Siegmund B, Le Berre C *et al.* Ulcerative colitis. *Nat Rev Dis Primers* 2020;**6**:74. https://doi.org/10.1038/s41572-020-0205-x.
3. Roda G, Chien Ng S, Kotze PG *et al.* Crohn's disease. *Nat Rev Dis Primers* 2020;**6**:22. https://doi.org/10.1038/s41572-020-0156-2.
4. Mak WY, Zhao M, Ng SC *et al.* The epidemiology of inflammatory bowel disease: east meets west. *J Gastroenterol Hepatol* 2020;**35**:380–9. https://doi.org/10.1111/jgh.14872.
5. Zhang YZ, Li YY. . Inflammatory bowel disease: pathogenesis. *World J Gastroenterol* 2014;**20**:91–9. https://doi.org/10.3748/wjg.v20.i1.91.
6. Khan MW, Kale AA, Bere P *et al.* Microbes, intestinal inflammation and probiotics. *Expert Rev Gastroenterol Hepatol* 2012;**6**:81–94. https://doi.org/10.1586/egh.11.94.
7. Gersemann M, Wehkamp J, Stange EF. Innate immune dysfunction in inflammatory bowel disease. *J Intern Med* 2012;**271**:421–8. https://doi.org/10.1111/j.1365-2796.2012.02515.x.
8. Bennike TB, Carlsen TG, Ellingsen T *et al.* Neutrophil extracellular traps in ulcerative colitis: A proteome analysis of intestinal biopsies. *Inflamm Bowel Dis* 2015;**21**:2052–67. https://doi.org/10.1097/MIB.0000000000000460.
9. Dinallo V, Marafini I, Di Fusco D *et al.* Neutrophil extracellular traps sustain inflammatory signals in ulcerative colitis. *J Crohns Colitis* 2019;**13**:772–84. https://doi.org/10.1093/ecco-jcc/jjy215.
10. Chen H, Wu X, Xu C *et al.* Dichotomous roles of neutrophils in modulating pathogenic and repair processes of inflammatory bowel diseases. *Precis Clin Med* 2021;**4**:246–57. https://doi.org/10.1093/pcmedi/pbab025.
11. Amarapurkar AD, Amarapurkar DN, Rathi P *et al.* Risk factors for inflammatory bowel disease: A prospective multi-center study. *Indian J Gastroenterol* 2018;**37**:189–95. https://doi.org/10.1007/s12664-018-0850-0.
12. Miner-Williams WM, Moughan PJ. Intestinal barrier dysfunction: implications for chronic inflammatory conditions of the bowel. *Nutr Res Rev* 2016;**29**:40–59. https://doi.org/10.1017/S0954422416000019.
13. Leppkes M, Neurath MF. Cytokines in inflammatory bowel diseases—Update 2020. *Pharmacol Res* 2020;**158**:104835. https://doi.org/10.1016/j.phrs.2020.104835.

14. Rutgeerts P, Sandborn WJ, Feagan BG *et al.* Infliximab for induction and maintenance therapy for ulcerative colitis. *N Engl J Med* 2005;**353**:2462–76. https://doi.org/10.1056/NEJMoa050516.
15. Torres J, Boyapati RK, Kennedy NA *et al.* Systematic review of effects of withdrawal of immunomodulators or biologic agents from patients with inflammatory bowel disease. *Gastroenterology* 2015;**149**:1716–30. https://doi.org/10.1053/j.gastro.2015.08.055.
16. Gisbert JP, Marin AC, Chaparro M. The risk of relapse after anti-tnf discontinuation in inflammatory bowel disease: systematic review and meta-analysis. *Am J Gastroenterol* 2016;**111**:632–47. https://doi.org/10.1038/ajg.2016.54.
17. Wang KC, Chang HY. Molecular mechanisms of long noncoding RNAs. *Mol Cell* 2011;**43**:904–14. https://doi.org/10.1016/j.molcel.2011.08.018.
18. Schmitz SU, Grote P, Herrmann BG. Mechanisms of long noncoding RNA function in development and disease. *Cell Mol Life Sci* 2016;**73**:2491–509. https://doi.org/10.1007/s00018-016-2174-5.
19. Mercer TR, Mattick JS. Structure and function of long noncoding RNAs in epigenetic regulation. *Nat Struct Mol Biol* 2013;**20**:300–7. https://doi.org/10.1038/nsmb.2480.
20. Rinn JL, Chang HY. Genome regulation by long noncoding RNAs. *Annu Rev Biochem* 2012;**81**:145–66. https://doi.org/10.1146/annurev-biochem-051410-092902.
21. Quinn JJ, Chang HY. Unique features of long non-coding RNA biogenesis and function. *Nat Rev Genet* 2016;**17**:47–62. https://doi.org/10.1038/nrg.2015.10.
22. Wu R, Su Y, Wu H *et al.* Characters, functions and clinical perspectives of long non-coding rnas. *Mol Genet Genomics* 2016;**291**:1013–33. https://doi.org/10.1007/s00438-016-1179-y.
23. de Goede OM, Nachun DC, Ferraro NM *et al.* Population-scale tissue transcriptomics maps long non-coding RNAs to complex disease. *Cell* 2021;**184**:2633–48. https://doi.org/10.1016/j.cell.2021.03.050.
24. Zacharopoulou E, Gazouli M, Tzouvala M *et al.* The contribution of long non-coding RNAs in inflammatory bowel diseases. *Dig Liver Dis* 2017;**49**:1067–72. https://doi.org/10.1016/j.dld.2017.08.003.
25. Wang YX, Lin C, Cui LJ *et al.* Mechanism of m2 macrophage-derived extracellular vesicles carrying lncRNA meg3 in inflammatory responses in ulcerative colitis. *Bioengineered* 2021;**12**:12722–39. https://doi.org/10.1080/21655979.2021.2010368.
26. Verdu EF, Galipeau HJ, Jabri B. Novel players in coeliac disease pathogenesis: role of the gut microbiota. *Nat Rev Gastroenterol Hepatol* 2015;**12**:497–506. https://doi.org/10.1038/nrgastro.2015.90.
27. Qiu P, Ishimoto T, Fu L *et al.* The gut microbiota in inflammatory bowel disease. *Front Cell Infect Microbiol* 2022;**12**:733992. https://doi.org/10.3389/fcimb.2022.733992.
28. Goll R, van Beelen Granlund A. Intestinal barrier homeostasis in inflammatory bowel disease. *Scand J Gastroenterol* 2015;**50**:3–12. https://doi.org/10.3109/00365521.2014.971425.
29. Antoni L, Nuding S, Wehkamp J *et al.* Intestinal barrier in inflammatory bowel disease. *World J Gastroenterol* 2014;**20**:1165–79. https://doi.org/10.3748/wjg.v20.i5.1165.
30. Chandran P, Satthaporn S, Robins A *et al.* Inflammatory bowel disease: dysfunction of galt and gut bacterial flora (i). *surg* 2003;**1**:63–75. https://doi.org/10.1016/s1479-666x(03)80118-x.
31. Kong S, Tao M, Shen X *et al.* Translatable circrnas and lncrnas: driving mechanisms and functions of their translation products. *Cancer Lett* 2020;**483**:59–65. https://doi.org/10.1016/j.canlet.2020.04.006.
32. Cesana M, Cacchiarelli D, Legnini I *et al.* A long noncoding RNA controls muscle differentiation by functioning as a competing endogenous RNA. *Cell* 2011;**147**:358–69. https://doi.org/10.1016/j.cell.2011.09.028.
33. Salmena L, Poliseno L, Tay Y *et al.* A cerna hypothesis: the rosetta stone of a hidden RNA language? *Cell* 2011;**146**:353–8. https://doi.org/10.1016/j.cell.2011.07.014.
34. Yoon JH, Abdelmohsen K, Srikantan S *et al.* Lincrna-p21 suppresses target mrna translation. *Mol Cell* 2012;**47**:648–55. https://doi.org/10.1016/j.molcel.2012.06.027.
35. Tripathi V, Ellis JD, Shen Z *et al.* The nuclear-retained noncoding rna malat1 regulates alternative splicing by modulating sr splicing factor phosphorylation. *Mol Cell* 2010;**39**:925–38. https://doi.org/10.1016/j.molcel.2010.08.011.
36. Gong C, Maquat LE. LncRNAs transactivate stau1-mediated mrna decay by duplexing with 3' utrs via alu elements. *Nature* 2011;**470**:284–8. https://doi.org/10.1038/nature09701.
37. Niu L, Lou F, Sun Y *et al.* A micropeptide encoded by lncRNA mir155hg suppresses autoimmune inflammation via modulating antigen presentation. *Sci Adv* 2020;**6**:eaaz2059. https://doi.org/10.1126/sciadv.aaz2059.
38. Li XL, Pongor L, Tang W *et al.* A small protein encoded by a putative lncRNA regulates apoptosis and tumorigenicity in human colorectal cancer cells. *Elife* 2020;**9**:e53734. https://doi.org/10.7554/eLife.53734.
39. Nelson BR, Makarewich CA, Anderson DM *et al.* A peptide encoded by a transcript annotated as long noncoding RNA enhances serca activity in muscle. *Science* 2016;**351**:271–5. https://doi.org/10.1126/science.aad4076.
40. Guo B, Wu S, Zhu X *et al.* Micropeptide cip2a-bp encoded by linc00665 inhibits triple-negative breast cancer progression. *EMBO J* 2020;**39**:e102190. https://doi.org/10.15252/embj.2019102190.
41. Wu S, Guo B, Zhang L *et al.* A micropeptide xbp1sbm encoded by lncrna promotes angiogenesis and metastasis of tnbc via xbp1s pathway. *Oncogene* 2022;**41**:2163–72. https://doi.org/10.1038/s41388-022-02229-6.
42. Qin J, Li R, Raes J *et al.* A human gut microbial gene catalogue established by metagenomic sequencing. *Nature* 2010;**464**:59–65. https://doi.org/10.1038/nature08821.
43. Baumgart DC, Sandborn WJ. Crohn's disease. *Lancet* 2012;**380**:1590–605. https://doi.org/10.1016/S0140-6736(12)60026-9.
44. Hillman ET, Lu H, Yao T *et al.* Microbial ecology along the gastrointestinal tract. *Microbes Environ* 2017;**32**:300–13. https://doi.org/10.1264/jsme2.ME17017.
45. Martinez C, Antolin M, Santos J *et al.* Unstable composition of the fecal microbiota in ulcerative colitis during clinical remission. *Am J Gastroenterol* 2008;**103**:643–8. https://doi.org/10.1111/j.1572-0241.2007.01592.x.
46. Wu X, Pan S, Luo W *et al.* Roseburia intestinalis–derived flagellin ameliorates colitis by targeting mir–223–3p–mediated activation of nlrp3 inflammasome and pyroptosis. *Mol Med Rep* 2020;**22**:2695–704. https://doi.org/10.3892/mmr.2020.11351.
47. Ruan G, Chen M, Chen L *et al.* Roseburia intestinalis and its metabolite butyrate inhibit colitis and upregulate tlr5 through the sp3 signaling pathway. *Nutrients* 2022;**14**:3041. https://doi.org/10.3390/nu14153041.
48. Xu F, Cheng Y, Ruan G *et al.* New pathway ameliorating ulcerative colitis: focus on roseburia intestinalis and the gut-brain

axis. *Therap Adv Gastroenterol* 2021;**14**:17562848211004469. https://doi.org/10.1177/17562848211004469.
49. Shen Z, Luo W, Tan B *et al.* Roseburia intestinalis stimulates tlr5-dependent intestinal immunity against crohn's disease. *EBioMedicine* 2022;**85**:104285. https://doi.org/10.1016/j.ebiom.2022.104285.
50. Xiao M, Shen Z, Luo W *et al.* A new colitis therapy strategy via the target colonization of magnetic nanoparticle-internalized roseburia intestinalis. *Biomater Sci* 2019;**7**:4174–85. https://doi.org/10.1039/c9bm00980a.
51. Quan Y, Song K, Zhang Y *et al.* Roseburia intestinalis-derived flagellin is a negative regulator of intestinal inflammation. *Biochem Biophys Res Commun* 2018;**501**:791–9. https://doi.org/10.1016/j.bbrc.2018.05.075.
52. Liu B, Sun L, Liu Q *et al.* A cytoplasmic nf-κb interacting long noncoding rna blocks iκb phosphorylation and suppresses breast cancer metastasis. *Cancer Cell* 2015;**27**:370–81. https://doi.org/10.1016/j.ccell.2015.02.004.
53. Lin JC, Ma XY, Liu JY *et al.* One gut microbiota, fusobacterium nucleatum aggravates neonatal necrotizing enterocolitis by induction of irf5 expression through lncRNA eno1-it1/mir-22-3p axis. *Eur Rev Med Pharmacol Sci* 2021;**25**:4714–28. https://doi.org/10.26355/eurrev_202107_26382.
54. Hong J, Guo F, Lu SY *et al.* Nucleatum targets lncRNA eno1-it1 to promote glycolysis and oncogenesis in colorectal cancer. *Gut* 2021;**70**:2123–37. https://doi.org/10.1136/gutjnl-2020-322780.
55. Braun T, Sosnovski KE, Amir A *et al.* Mucosal transcriptomics highlight lncRNAs implicated in ulcerative colitis, crohn disease, and celiac disease. *JCI Insight* 2023;**8**. https://doi.org/10.1172/jci.insight.170181.
56. Liang LX, Ai LY, Qian J *et al.* Long noncoding RNA expression profiles in gut tissues constitute molecular signatures that reflect the types of microbes. *Sci Rep* 2015;**5**:11763. https://doi.org/10.1038/srep11763.
57. Dempsey J, Zhang A, Cui JY. Coordinate regulation of long noncoding rnas and protein-coding genes in germ-free mice. *Bmc Genomics [Electronic Resource]* 2018;**19**:834. https://doi.org/10.1186/s12864-018-5235-3.
58. Hapfelmeier S, Lawson MA, Slack E *et al.* Reversible microbial colonization of germ-free mice reveals the dynamics of iga immune responses. *Science* 2010;**328**:1705–9. https://doi.org/10.1126/science.1188454.
59. Vaishnava S, Yamamoto M, Severson KM *et al.* The antibacterial lectin regiiigamma promotes the spatial segregation of microbiota and host in the intestine. *Science* 2011;**334**:255–8. https://doi.org/10.1126/science.1209791.
60. Ismail AS, Severson KM, Vaishnava S *et al.* Gammadelta intraepithelial lymphocytes are essential mediators of host-microbial homeostasis at the intestinal mucosal surface. *Proc Natl Acad Sci U S A* 2011;**108**:8743–8. https://doi.org/10.1073/pnas.1019574108.
61. Sommer F, Backhed F. The gut microbiota—Masters of host development and physiology. *Nat Rev Microbiol* 2013;**11**:227–38. https://doi.org/10.1038/nrmicro2974.
62. Wibowo AA, Pardjianto B, Sumitro SB *et al.* Decreased expression of muc2 due to a decrease in the expression of lectins and apoptotic defects in colitis patients. *Biochem Biophys Rep* 2019;**19**:100655. https://doi.org/10.1016/j.bbrep.2019.100655.
63. Ma S, Yeom J, Lim YH. Dairy propionibacterium freudenreichii ameliorates acute colitis by stimulating muc2 expression in intestinal goblet cell in a dss-induced colitis rat model. *Sci Rep* 2020;**10**:5523. https://doi.org/10.1038/s41598-020-62497-8.
64. Kim MW, Choi S, Kim SY *et al.* Allyl isothiocyanate ameliorates dextran sodium sulfate-induced colitis in mouse by enhancing tight junction and mucin expression. *Int J Mol Sci* 2018;**19**:2025. https://doi.org/10.3390/ijms19072025.
65. Tytgat KM, van der Wal JW, Einerhand AW *et al.* Quantitative analysis of muc2 synthesis in ulcerative colitis. *Biochem Biophys Res Commun* 1996;**224**:397–405. https://doi.org/10.1006/bbrc.1996.1039.
66. Zhang X, Ma L, Zhang C *et al.* Silencing lncrna-dancr attenuates inflammation and dss-induced endothelial injury through mir-125b-5p. *Gastroenterol Hepatol* 2021;**44**:644–53. https://doi.org/10.1016/j.gastrohep.2020.10.008.
67. Kayama H, Okumura R, Takeda K. Interaction between the microbiota, epithelia, and immune cells in the intestine. *Annu Rev Immunol* 2020;**38**:23–48. https://doi.org/10.1146/annurev-immunol-070119-115104.
68. Kinnebrew MA, Buffie CG, Diehl GE *et al.* Interleukin 23 production by intestinal cd103(+)cd11b(+) dendritic cells in response to bacterial flagellin enhances mucosal innate immune defense. *Immunity* 2012;**36**:276–87. https://doi.org/10.1016/j.immuni.2011.12.011.
69. Menard S, Cerf-Bensussan N, Heyman M. Multiple facets of intestinal permeability and epithelial handling of dietary antigens. *Mucosal Immunol* 2010;**3**:247–59. https://doi.org/10.1038/mi.2010.5.
70. Chiba H, Osanai M, Murata M *et al.* Transmembrane proteins of tight junctions. *Biochim Biophys Acta* 2008;**1778**:588–600. https://doi.org/10.1016/j.bbamem.2007.08.017.
71. Huang S, Fu Y, Xu B *et al.* Wogonoside alleviates colitis by improving intestinal epithelial barrier function via the mlck/pmlc2 pathway. *Phytomedicine* 2020;**68**:153179. https://doi.org/10.1016/j.phymed.2020.153179.
72. Li W, Gao M, Han T. Lycium barbarum polysaccharides ameliorate intestinal barrier dysfunction and inflammation through the mlck-mlc signaling pathway in caco-2 cells. *Food Funct* 2020;**11**:3741–8. https://doi.org/10.1039/d0fo00030b.
73. Zhang S, Xu W, Wang H *et al.* Inhibition of creb-mediated zo-1 and activation of nf-kappab-induced il-6 by colonic epithelial mct4 destroys intestinal barrier function. *Cell Prolif* 2019;**52**:e12673. https://doi.org/10.1111/cpr.12673.
74. Ma D, Cao Y, Wang Z *et al.* Ccat1 lncRNA promotes inflammatory bowel disease malignancy by destroying intestinal barrier via downregulating mir-185-3p. *Inflamm Bowel Dis* 2019;**25**:862–74. https://doi.org/10.1093/ibd/izy381.
76. Zou T, Jaladanki SK, Liu L *et al.* H19 long noncoding RNA regulates intestinal epithelial barrier function via microrna 675 by interacting with RNA-binding protein hur. *Mol Cell Biol* 2016;**36**:1332–41. https://doi.org/10.1128/MCB.01030-15.
77. Chen T, Xue H, Lin R *et al.* Mir-34c and plncrna1 mediated the function of intestinal epithelial barrier by regulating tight junction proteins in inflammatory bowel disease. *Biochem Biophys Res Commun* 2017;**486**:6–13. https://doi.org/10.1016/j.bbrc.2017.01.115.
78. Liu R, Tang A, Wang X *et al.* Inhibition of lncRNA neat1 suppresses the inflammatory response in ibd by modulating the intestinal epithelial barrier and by exosome-mediated polarization of macrophages. *Int J Mol Med* 2018;**42**:2903–13. https://doi.org/10.3892/ijmm.2018.3829.
79. Rankin CR, Lokhandwala ZA, Huang R *et al.* Linear and circular cdkn2b-as1 expression is associated with

inflammatory bowel disease and participates in intestinal barrier formation. *Life Sci* 2019;**231**:116571. https://doi.org/10.1016/j.lfs.2019.116571.
80. Li Y, Zhu L, Chen P *et al.* Malat1 maintains the intestinal mucosal homeostasis in Crohn's disease via the mir-146b-5p-cldn11/numb pathway. *J Crohns Colitis* 2021;**15**:1542–57. https://doi.org/10.1093/ecco-jcc/jjab040.
81. Qiu W, Wu B, Wang X *et al.* Puma-mediated intestinal epithelial apoptosis contributes to ulcerative colitis in humans and mice. *J Clin Invest* 2011;**121**:1722–32. https://doi.org/10.1172/JCI42917.
82. Eissa N, Hussein H, Diarra A *et al.* Semaphorin 3e regulates apoptosis in the intestinal epithelium during the development of colitis. *Biochem Pharmacol* 2019;**166**:264–73. https://doi.org/10.1016/j.bcp.2019.05.029.
83. Araki Y, Mukaisyo K, Sugihara H *et al.* Increased apoptosis and decreased proliferation of colonic epithelium in dextran sulfate sodium-induced colitis in mice. *Oncol Rep* 2010;**24**:869–74. https://doi.org/10.3892/or.2010.869.
84. Qiao C, Yang L, Wan J *et al.* Long noncoding RNA anril contributes to the development of ulcerative colitis by mir-323b-5p/tlr4/myd88/nf-kappab pathway. *Biochem Biophys Res Commun* 2019;**508**:217–24. https://doi.org/10.1016/j.bbrc.2018.11.100.
85. Lei N, Kong P, Chen S *et al.* Upregulated norad is implicated in apoptosis, inflammation, and oxidative stress in ulcerative colitis through the nuclear factor-kappaappab signaling. *Eur J Gastroenterol Hepatol* 2022;**34**:630–9. https://doi.org/10.1097/MEG.0000000000002370.
86. Xu Y, Zhang L, Ocansey DKW *et al.* Hucmsc-ex alleviates inflammatory bowel disease via the lnc78583-mediated mir3202/hoxb13 pathway. *J Zhejiang Univ Sci B* 2022;**23**:423–31. https://doi.org/10.1631/jzus.B2100793.
87. Pan S, Liu R, Wu X *et al.* LncRNA neat1 mediates intestinal inflammation by regulating tnfrsf1b. *Ann Transl Med* 2021;**9**:773. https://doi.org/10.21037/atm-21-34.
88. Padua D, Mahurkar-Joshi S, Law IK *et al.* A long noncoding RNA signature for ulcerative colitis identifies ifng-as1 as an enhancer of inflammation. *Am J Physiol Gastrointest Liver Physiol* 2016;**311**:G446–57. https://doi.org/10.1152/ajpgi.00212.2016.
89. Fouad MR, Salama RM, Zaki HF *et al.* Vildagliptin attenuates acetic acid-induced colitis in rats via targeting pi3k/akt/nfkappab, nrf2 and creb signaling pathways and the expression of lncrna ifng-as1 and mir-146a. *Int Immunopharmacol* 2021;**92**:107354. https://doi.org/10.1016/j.intimp.2020.107354.
90. Lucafo M, Pugnetti L, Bramuzzo M *et al.* Long non-coding RNA GAS5 and intestinal MMP2 and MMP9 expression: A translational study in pediatric patients with IBD. *Int J Mol Sci* 2019;**20**:5280. https://doi.org/10.3390/ijms20215280.
91. Ye M, Wang C, Zhu J *et al.* An nf-kappab-responsive long noncoding RNA, pint, regulates tnf-alpha gene transcription by scaffolding p65 and ezh2. *FASEB J* 2021;**35**:e21667. https://doi.org/10.1096/fj.202002263R.
92. Akincilar SC, Wu L, Ng QF *et al.* Nail: an evolutionarily conserved lncrna essential for licensing coordinated activation of p38 and nfkappab in colitis. *Gut* 2021;**70**:1857–71. https://doi.org/10.1136/gutjnl-2020-322980.
93. Zhu M, Xie J. LncRNA malat1 promotes ulcerative colitis by upregulating lncRNA anril. *Dig Dis Sci* 2020;**65**:3191–6. https://doi.org/10.1007/s10620-020-06093-w.
94. Li F, Liu H, Fu J *et al.* Knockdown of long non-coding RNA neat1 relieves inflammation of ulcerative colitis by regulating the mir-603/fgf9 pathway. *Exp Ther Med* 2022;**23**:131. https://doi.org/10.3892/etm.2021.11054.
95. Deng B, Lv W, Duan W *et al.* Fgf9 modulates schwann cell myelination in developing nerves and induces a pro-inflammatory environment during injury. *J Cell Biochem* 2018;**119**:8643–58. https://doi.org/10.1002/jcb.27105.
96. Yin Y, Ornitz DM. FGF9 and FGF10 activate distinct signaling pathways to direct lung epithelial specification and branching. *Sci Signal* 2020;**13**:eaay4353. https://doi.org/10.1126/scisignal.aay4353.
97. Wang K, Zhang Z, Liu K *et al.* Neat1-mirna204-5p-pi3k-akt axis as a potential mechanism for photodynamic therapy treated colitis in mice. *Photodiagnosis Photodyn Ther* 2018;**24**:349–57. https://doi.org/10.1016/j.pdpdt.2018.10.020.
98. Ding G, Ming Y, Zhang Y. LncRNA mirt2 is downregulated in ulcerative colitis and regulates il-22 expression and apoptosis in colonic epithelial cells. *Gastroenterol Res Pract* 2019;**2019**:8154692. https://doi.org/10.1155/2019/8154692.
99. Xia H, Li S, He Y *et al.* Long non-coding RNA anril serves as a potential marker of disease risk, inflammation, and disease activity of pediatric inflammatory bowel disease. *Clin Res Hepatol Gastroenterol* 2022;**46**:101895. https://doi.org/10.1016/j.clinre.2022.101895.
100. Tian Y, Cui L, Lin C *et al.* LncRNA cdkn2b-as1 relieved inflammation of ulcerative colitis via sponging mir-16 and mir-195. *Int Immunopharmacol* 2020;**88**:106970. https://doi.org/10.1016/j.intimp.2020.106970.
101. Ni S, Liu Y, Zhong J *et al.* Inhibition of lncRNA-neat1 alleviates intestinal epithelial cells (IECs) dysfunction in ulcerative colitis by maintaining the homeostasis of the glucose metabolism through the mir-410-3p-ldha axis. *Bioengineered* 2022;**13**:8961–71. https://doi.org/10.1080/21655979.2022.2037957.
102. Han J, Li Y, Zhang B *et al.* LncRNA tug1 regulates ulcerative colitis through mir-142-5p/socs1 axis. *Microb Pathog* 2020;**143**:104139. https://doi.org/10.1016/j.micpath.2020.104139.
103. Piganis RA, De Weerd NA, Gould JA *et al.* Suppressor of cytokine signaling (SOCS) 1 inhibits type I interferon (IFN) signaling via the interferon alpha receptor (IFNAR1)-associated tyrosine kinase Tyk2. *J Biol Chem* 2011;**286**:33811–8. https://doi.org/10.1074/jbc.M111.270207.
104. Tian Y, Wang Y, Li F *et al.* LncRNA tug1 regulates the balance of hur and mir-29b-3p and inhibits intestinal epithelial cell apoptosis in a mouse model of ulcerative colitis. *Hum Cell* 2021;**34**:37–48. https://doi.org/10.1007/s13577-020-00428-5.
105. Wang Y, Wang N, Cui L *et al.* Long non-coding RNA meg3 alleviated ulcerative colitis through upregulating mir-98-5p-sponged il-10. *Inflammation* 2021;**44**:1049–59. https://doi.org/10.1007/s10753-020-01400-z
106. Lv Q, Shi C, Qiao S *et al.* Alpinetin exerts anti-colitis efficacy by activating ahr, regulating mir-302/dnmt-1/creb signals, and therefore promoting treg differentiation. *Cell Death Dis* 2018;**9**:890. https://doi.org/10.1038/s41419-018-0814-4.
107. Li K, Yang J, Lei XF *et al.* Ezh2 inhibition promotes angptl4/creb1 to suppress the progression of ulcerative colitis. *Life Sci* 2020;**250**:117553. https://doi.org/10.1016/j.lfs.2020.117553.
108. Li H, Xuan J, Zhang W *et al.* Long non-coding RNA snhg5 regulates ulcerative colitis via microrna-375/janus kinase-2 axis. *Bioengineered* 2021;**12**:4150–8. https://doi.org/10.1080/21655979.2021.1953219.
109. Zhao ML, Chen T, Zhang TH *et al.* H19 overexpression improved efficacy of mesenchymal stem cells in ulcerative

colitis by modulating the mir-141/icam-1 and mir-139/cxcr4 axes. *Dis Markers* 2021;**2021**:7107705. https://doi.org/10.1155/2021/7107705.
110. Yin L, Yan J, Chen W. Mechanism of lncRNA-h19 in intestinal injury of mice with ulcerative colitis. *Int Arch Allergy Immunol* 2022;**183**:985–96. https://doi.org/10.1159/000524156.
111. Yang F, Li XF, Cheng LN *et al.* Long non-coding RNA crnde promotes cell apoptosis by suppressing mir-495 in inflammatory bowel disease. *Exp Cell Res* 2019;**382**:111484. https://doi.org/10.1016/j.yexcr.2019.06.029.
112. Yao J, Gao R, Luo M *et al.* Long noncoding RNA kif9-as1 promotes cell apoptosis by targeting the microrna-148a-3p/suppressor of cytokine signaling axis in inflammatory bowel disease. *Eur J Gastroenterol Hepatol* 2021;**33**:e922–e32. https://doi.org/10.1097/MEG.0000000000002309.
113. Fang L, Hu M, Xia F *et al.* Linc01272 activates epithelial-mesenchymal transition through mir-153-5p in Crohn's disease. *Am J Transl Res* 2022;**14**:2331–42
114. Mirza AH, Berthelsen CH, Seemann SE *et al.* Transcriptomic landscape of lncRNAs in inflammatory bowel disease. *Genome Med* 2015;**7**:39. https://doi.org/10.1186/s13073-015-0162-2.
115. Yu T, Meng F, Xie M *et al.* Long noncoding RNA pms2l2 downregulates mir-24 through methylation to suppress cell apoptosis in ulcerative colitis. *Dig Dis* 2021;**39**:467–76. https://doi.org/10.1159/000513330.
116. Wu F, Huang Y, Dong F *et al.* Ulcerative colitis-associated long noncoding RNA, bc012900, regulates intestinal epithelial cell apoptosis. *Inflamm Bowel Dis* 2016;**22**:782–95. https://doi.org/10.1097/MIB.0000000000000691.
117. Feng X, Xiao Y, He J *et al.* Long noncoding RNA gm31629 protects against mucosal damage in experimental colitis via yb-1/e2f pathway. *JCI Insight* 2022;**7**:e150091. https://doi.org/10.1172/jci.insight.150091.
118. Tatiya-Aphiradee N, Chatuphonprasert W, Jarukamjorn K. Immune response and inflammatory pathway of ulcerative colitis. *J Basic Clin Physiol Pharmacol* 2018;**30**:1–10. https://doi.org/10.1515/jbcpp-2018-0036.
119. Neurath MF. Cytokines in inflammatory bowel disease. *Nat Rev Immunol* 2014;**14**:329–42. https://doi.org/10.1038/nri3661.
120. Kmiec Z, Cyman M, Slebioda TJ. Cells of the innate and adaptive immunity and their interactions in inflammatory bowel disease. *Adv Med Sci* 2017;**62**:1–16. https://doi.org/10.1016/j.advms.2016.09.001.
121. Wu J, Zhang H, Zheng Y *et al.* The long noncoding rna malat1 induces tolerogenic dendritic cells and regulatory t cells via mir155/dendritic cell-specific intercellular adhesion molecule-3 grabbing nonintegrin/il10 axis. *Front Immunol* 2018;**9**:1847. https://doi.org/10.3389/fimmu.2018.01847.
122. Feng S, Xu Z, Zhang Z *et al.* RNA-seq approach to investigate the effects of melatonin on bone marrow-derived dendritic cells from dextran sodium sulfate-induced colitis mice. *Toxicology* 2022;**481**:153354. https://doi.org/10.1016/j.tox.2022.153354.
123. Wang Y, Zhao M, Liu S *et al.* Macrophage-derived extracellular vesicles: diverse mediators of pathology and therapeutics in multiple diseases. *Cell Death Dis* 2020;**11**:924. https://doi.org/10.1038/s41419-020-03127-z.
124. Muthas D, Reznichenko A, Balendran CA *et al.* Neutrophils in ulcerative colitis: A review of selected biomarkers and their potential therapeutic implications. *Scand J Gastroenterol* 2017;**52**:125–35. https://doi.org/10.1080/00365521.2016.1235224.
125. Lu JW, Rouzigu A, Teng LH *et al.* The construction and comprehensive analysis of inflammation-related ceRNA networks and tissue-infiltrating immune cells in ulcerative progression. *Biomed Res Int* 2021;**2021**:6633442. https://doi.org/10.1155/2021/6633442.
126. Yin S, Li X, Xiong Z *et al.* A novel ceRNA-immunoregulatory axis based on immune cell infiltration in ulcerative colitis-associated colorectal carcinoma by integrated weighted gene co-expression network analysis. *BMC Gastroenterol* 2022;**22**:188. https://doi.org/10.1186/s12876-022-02252-7.
127. Artis D, Spits H. The biology of innate lymphoid cells. *Nature* 2015;**517**:293–301. https://doi.org/10.1038/nature14189.
128. Serafini N, Klein Wolterink RG, Satoh-Takayama N *et al.* Gata3 drives development of rorgammat+ group 3 innate lymphoid cells. *J Exp Med* 2014;**211**:199–208. https://doi.org/10.1084/jem.20131038.
129. Liu B, Ye B, Yang L *et al.* Long noncoding RNA lnckdm2b is required for ilc3 maintenance by initiation of zfp292 expression. *Nat Immunol* 2017;**18**:499–508. https://doi.org/10.1038/ni.3712.
130. Eken A, Singh AK, Treuting PM *et al.* Il-23r+ innate lymphoid cells induce colitis via interleukin-22-dependent mechanism. *Mucosal Immunol* 2014;**7**:143–54. https://doi.org/10.1038/mi.2013.33.
131. Nguyen HT, Lapaquette P, Bringer MA *et al.* Autophagy and Crohn's disease. *J Innate Immun* 2013;**5**:434–43. https://doi.org/10.1159/000345129.
132. Larabi A, Barnich N, Nguyen HTT. New insights into the interplay between autophagy, gut microbiota and inflammatory responses in IBD. *Autophagy* 2020;**16**:38–51. https://doi.org/10.1080/15548627.2019.1635384.
133. Yu TX, Chung HK, Xiao L *et al.* Long noncoding RNA h19 impairs the intestinal barrier by suppressing autophagy and lowering paneth and goblet cell function. *Cell Mol Gastroenterol Hepatol* 2020;**9**:611–25. https://doi.org/10.1016/j.jcmgh.2019.12.002.
134. Cadwell K, Liu JY, Brown SL *et al.* A key role for autophagy and the autophagy gene atg16l1 in mouse and human intestinal paneth cells. *Nature* 2008;**456**:259–63. https://doi.org/10.1038/nature07416.
135. Ji E, Kim C, Kang H *et al.* RNA binding protein hur promotes autophagosome formation by regulating expression of autophagy-related proteins 5, 12, and 16 in human hepatocellular carcinoma cells. *Mol Cell Biol* 2019;**39**:e00508–18. https://doi.org/10.1128/MCB.00508-18.
136. Xiao L, Rao JN, Wang JY. RNA-binding proteins and long noncoding RNAs in intestinal epithelial autophagy and barrier function. *Tissue Barriers* 2021;**9**:1895648. https://doi.org/10.1080/21688370.2021.1895648.
137. Fuss IJ, Neurath M, Boirivant M *et al.* Disparate CD4+ lamina propria (LP) lymphokine secretion profiles in inflammatory bowel disease. Crohn's disease LP cells manifest increased secretion of IFN-gamma, whereas ulcerative colitis LP cells manifest increased secretion of IL-5. *J Immunol* 1996;**157**:1261–70. https://doi.org/10.4049/jimmunol.157.3.1261.
138. Yang W, Yu T, Cong Y. $CD4^+$ T cell metabolism, gut microbiota, and autoimmune diseases: implication in precision medicine of autoimmune diseases. *Precis Clin Med* 2022;**5**:pbac018. https://doi.org/10.1093/pcmedi/pbac018.
139. Braga-Neto MB, Gaballa JM, Bamidele AO *et al.* Deregulation of long intergenic non-coding rnas in CD4+ T cells of lamina propria in Crohn's disease through transcriptome profiling. *J Crohns Colitis* 2020;**14**:96–109. https://doi.org/10.1093/ecco-jcc/jjz109.
140. Nie J, Zhao Q. Lnc-itsn1-2, derived from RNA sequencing, correlates with increased disease risk, activity and promotes CD4(+)

T cell activation, proliferation and th1/th17 cell differentiation by serving as a cerna for il-23r via sponging mir-125a in inflammatory bowel disease. *Front Immunol* 2020;**11**:852. https://doi.org/10.3389/fimmu.2020.00852.
141. Rankin CR, Shao L, Elliott J *et al.* The IBD-associated long noncoding RNA IFNG-AS1 regulates the balance between inflammatory and anti-inflammatory cytokine production after T-cell stimulation. *Am J Physiol Gastrointest Liver Physiol* 2020;**318**:G34–40. https://doi.org/10.1152/ajpgi.00232.2019.
142. Kanhere A, Hertweck A, Bhatia U *et al.* T-bet and gata3 orchestrate th1 and th2 differentiation through lineage-specific targeting of distal regulatory elements. *Nat Commun* 2012;**3**:1268. https://doi.org/10.1038/ncomms2260.
143. Qiao YQ, Huang ML, Xu AT *et al.* LncRNA dq786243 affects treg related creb and foxp3 expression in Crohn's disease. *J Biomed Sci* 2013;**20**:87. https://doi.org/10.1186/1423-0127-20-87.
144. Kim HP, Leonard WJ. Creb/atf-dependent T cell receptor-induced foxp3 gene expression: A role for DNA methylation. *J Exp Med* 2007;**204**:1543–51. https://doi.org/10.1084/jem.20070109.
145. Zhang L, Zhao Y. The regulation of foxp3 expression in regulatory CD4(+)CD25(+)T cells: multiple pathways on the road. *J Cell Physiol* 2007;**211**:590–7. https://doi.org/10.1002/jcp.21001.
146. Li N, Shi R. Expression alteration of long non-coding RNAs and their target genes in the intestinal mucosa of patients with Crohn's disease. *Clin Chim Acta* 2019;**494**:14–21. https://doi.org/10.1016/j.cca.2019.02.031.
147. Zhu C, Fan M, Zhu J *et al.* Vitamin D reduces the helper T cells 17 (th17) differentiation in patients with ulcerative colitis by targeting long non-coding RNA (lncRNA) oip5-as1/mir-26a-5p/il-6 axis. *Iran J Immunol* 2022;**19**:150–60. https://doi.org/10.22034/iji.2022.90562.2014.
148. Wang XJ, Li XY, Guo XC *et al.* LncRNA-miRNA-mRNA network analysis reveals the potential biomarkers in Crohn's disease rats treated with herb-partitioned moxibustion. *J Inflamm Res* 2022;**15**:1699–716. https://doi.org/10.2147/JIR.S351672.
149. Yarani R, Mirza AH, Kaur S *et al.* The emerging role of lncRNAs in inflammatory bowel disease. *Exp Mol Med* 2018;**50**:1–14. https://doi.org/10.1038/s12276-018-0188-9.
150. Lin L, Zhou G, Chen P *et al.* Which long noncoding RNAs and circular RNAs contribute to inflammatory bowel disease? *Cell Death Dis* 2020;**11**:456. https://doi.org/10.1038/s41419-020-2657-z.
151. Ghafouri-Fard S, Eghtedarian R, Taheri M. The crucial role of non-coding RNAs in the pathophysiology of inflammatory bowel disease. *Biomed Pharmacother* 2020;**129**:110507. https://doi.org/10.1016/j.biopha.2020.110507.
152. Li C, Cui L, Li S *et al.* Long non-coding RNA mirt2 interacts with long non-coding RNA IFNG-AS1 to regulate ulcerative colitis. *Exp Ther Med* 2020;**20**:32. https://doi.org/10.3892/etm.2020.9159.
153. Wang S, Hou Y, Chen W *et al.* Kif9–as1, linc01272 and dio3os lncRNAs as novel biomarkers for inflammatory bowel disease. *Mol Med Rep* 2018;**17**:2195–202. https://doi.org/10.3892/mmr.2017.8118.
154. Ge Q, Dong Y, Lin G *et al.* Long noncoding RNA antisense noncoding RNA in the ink4 locus correlates with risk, severity, inflammation and infliximab efficacy in Crohn's disease. *Am J Med Sci* 2019;**357**:134–42. https://doi.org/10.1016/j.amjms.2018.10.016.
155. Shaker OG, Ali MA, Ahmed TI *et al.* Association between linc00657 and mir-106a serum expression levels and susceptibility to colorectal cancer, adenomatous polyposis, and ulcerative colitis in Egyptian population. *IUBMB Life* 2019;**71**:1322–35. https://doi.org/10.1002/iub.2039.
156. Lucafo M, Di Silvestre A, Romano M *et al.* Role of the long non-coding RNA growth arrest-specific 5 in glucocorticoid response in children with inflammatory bowel disease. *Basic Clin Pharmacol Toxicol* 2018;**122**:87–93. https://doi.org/10.1111/bcpt.12851.
157. Wu G, Zhang J, Zhao Q *et al.* Molecularly engineered macrophage-derived exosomes with inflammation tropism and intrinsic heme biosynthesis for atherosclerosis treatment. *Angew Chem Int Ed Engl* 2020;**59**:4068–74. https://doi.org/10.1002/anie.201913700.
158. Deng F, Yan J, Lu J *et al.* M2 macrophage-derived exosomal mir-590-3p attenuates dss-induced mucosal damage and promotes epithelial repair via the lats1/yap/beta-catenin signalling axis. *J Crohns Colitis* 2021;**15**:665–77. https://doi.org/10.1093/ecco-jcc/jjaa214.
159. Wu H, Fan H, Shou Z *et al.* Extracellular vesicles containing mir-146a attenuate experimental colitis by targeting traf6 and irak1. *Int Immunopharmacol* 2019;**68**:204–12. https://doi.org/10.1016/j.intimp.2018.12.043.
160. Yang J, Zhou CZ, Zhu R *et al.* Mir-200b-containing microvesicles attenuate experimental colitis associated intestinal fibrosis by inhibiting epithelial-mesenchymal transition. *J Gastroenterol Hepatol* 2017;**32**:1966–74. https://doi.org/10.1111/jgh.13797.

Received 18 September 2023; accepted 6 December 2023. **Published:** 11 December 2023