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REVIEW ARTICLE

Updated immunomodulatory roles of gut flora and microRNAs in inflammatory bowel diseases

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Abstract
Inflammatory bowel disease is a heterogeneous intestinal inflammatory disorder, including ulcerative colitis (UC) and Crohn's disease (CD). Existing studies have shown that the pathogenesis of IBD is closely related to the host's genetic susceptibility, intestinal flora disturbance and mucosal immune abnormalities, etc. It is generally believed that there are complicated interactions between host immunity and intestinal microflora/microRNAs during the occurrence and progression of IBD. Intestinal flora is mainly composed of bacteria, fungi, viruses and helminths. These commensals are highly implicated in the maintenance of intestinal microenvironment homeostasis alone or in combination. MiRNA is an endogenous non-coding small RNA with a length of 20 to 22 nucleotides, which can perform a variety of biological functions by silencing or activating target genes through complementary pairing bonds. A large quantity of miRNAs are involved in intestinal inflammation, mucosal barrier integrity, autophagy, vesicle transportation and other small RNA alterations in IBD circumstance. In this review, the immunomodulatory roles of gut flora and microRNAs are updated in the occurrence and progression of IBD. Meanwhile, the gut flora and microRNA targeted therapeutic strategies as well as other immunomodulatory approaches including TNF-α monoclonal antibodies are also emphasized in the treatment of IBD.

Keywords Inflammatory bowel disease · MicroRNA · Immune response · Gut flora · Immunotherapy

Distribution, manifestation and pathogenesis of IBD

The term "inflammatory bowel disease (IBD)" was firstly brought up by Matthew Baillie in 1793 and narrowly refers to ulcerative colitis (UC) at the beginning [1]. Currently, IBD is described as a recurrent and recalcitrant chronic inflammation in gastrointestinal tract, commonly including Crohn′s disease (CD) and UC. CD is a chronic and relapsing intestinal disorder that typically has a manifestation of abdominal pain, fever, and bloody or non-bloody diarrhea [2]. The reported annual incidence of CD is, respectively, 13.9/100000 in North America and 12.3/100000 in Europe [3]. UC is also a chronic gut disease characterized by diffuse mucosa inflammation of the colon and rectum, whose hallmark clinical symptom is bloody diarrhea [4]. In Asia, approximately 5.3 to 63.6 per 100,000 people suffer from this disease, while in North America, the proportion increases to 37.5 to 238 [5]. Multiple causative factors including abnormal abundance and diversity of gut organisms, altered miRNA profiling, and dysregulated immune responses influence the occurrence and progression of IBD.

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Intestinal flora and IBD

Roles of intestinal bacteria in IBD

Over the past decades, increasing evidence has highlighted the tremendous impact of gut bacterial flora or microbiota on human health. Human intestinal bacterial flora consists

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of *Firmicutes*, *Bacteroidetes*, *Proteobacteria, Actinobacteria*, *Verrucobacteria*, *Fusobacteria* and unclassified near *Cyanobacteria* as reported in an EU human gut flora project initiated in 2002 [6]. The commensal gut microbiota is featured by high diversity, stability, resistance, and resilience, whereas dysregulated gut microbiomes exhibit lower relative abundance and loss of symbiosis and diversity. A great number of reports demonstrate that intestinal bacterial imbalance is a pivotal factor to affect the severity of IBD. Generally, the microbiota of patients with IBD show a remarkable decrease in the abundance of *Bacteroidetes* and *Firmicutes*, and a prominent increase in the proportion of *Proteobacteria* and *Actinobacteria* [7]. Gut bacteria have multiple virulence factors to exert adverse effects on IBD. A variety of invasive bacteria, such as *Escherichia coli* and *Bacteroides fragilis*, can propagate and generate enterobactin toxin (ENT) and *Bacteroides fragilis* toxin (BFT) in the blood, causing acute or chronic inflammation-related systemic symptoms in intestinal mucosa and IBD aggravation [8, 9]. The immunosuppressive proteins (Hsp 60, Hsp 65) produced by several pathogenic bacteria can dysregulate intestinal mucosal immune response [10, 11]. As a self-defensive agglomerate, bacterial biofilms are protective of themselves from immune recognition and elimination, thereby enhancing the severity of IBD [12]. Besides pathogenic bacterial commensals, there are a group of beneficial bacteria called probiotics that are conducive to maintaining gut homeostasis by counteracting abnormal colonization and proliferation of pathogenic bacteria. For example, IBD patients have declined bacterial species producing butyrate, a short-chain fatty acid that can positively regulate intestinal function and reduce inflammation [13].

Roles of intestinal fungi in IBD

In the gut, commensal fungal flora or mycobiota is another large group of gut communities that keep intestinal ecosystem normal and functional. Although fungi is a tiny constituent of the whole intestinal flora, accounting for nearly 0.02 and 0.03% of mucosal and fecal microorganisms, respectively, they are widely involved in a variety of human diseases [14]. Based on internal transcribed spacer (ITS) region sequencing in 18S rRNA, intestinal fungi are mainly composed of *Basidiomycota*, *Ascomycota*, and *Chytridiomycota*, and the majority of fungal species mainly consist of *Candida* spp., *Aspergillus* spp., *Cryptococcus* spp., *Mucor* spp., *Rhodotorula* spp., *Penicillium* spp., *Debaryomyces* spp. and *Trichosporon* spp. [15]. Increasing cases appear to suggest that mycobiota dysbiosis is a key inducing factor in IBD progression. In IBD patients, the gut fungi display a skewed distribution with an increased ratio of *Basidiomycetes* to *Ascomycetes* [16]. *Candida* spp., for example *C. abicans*, *C. tropicalis*, and *C. glabrata*, are a cluster of most commonly encountered *Ascomycetes* in the human gut. Several types of *Candida* spp. (such as *C. abicans*) have an ability of yeast-to-hypha transition and can readily colonize intestinal mucosa followed by hyphae mediated invasion across host mucosal barrier [17]. A number of animal and human experiments display the increased ratio of *Candida* spp. in IBD settings [17–19]. Besides hypha, *Candida* species can take advantage of candidalysin, extracellular phospholipase, secreted aspartyl proteinase, and hemolysin to exacerbate colitis [20, 21]. The corrected abundance of *Candida* spp. can mitigate IBD and improve intestinal malfunctions [22]. There are also other intestinal fungi including *Cryptococcus neoformans*, *Malassezia restricta elicits*, *Aspergillus sydowii*, *Trichosporon pullulans* that can produce diverse virulence factors (capsule, mycotoxins, hypha, etc.) to intensify IBD [23–29]. Alike to beneficial bacteria, some gut probiotic fungi, such as *Saccharomyces boulardii*, can alleviate IBD through protecting intestinal barrier integrity, preventing pathogen colonization and invasion, and regulating anti-inflammatory levels [30].

Roles of intestinal viruses in IBD

With the rapid development of high-throughput sequencing technology, viral microorganisms in the gut have attracted widespread attention. Viruses are the most abundant microbes in the gut, and they account for 10 times that of bacteria [31]. The majority of human enteroviruses belong to bacteriophages (95%) and eukaryotic viruses. Bacteriophages consist of dsDNA *Caudovirales* order including *Siphoviridae, Myoviridae, Podoviridae, Herelleviridae*, *Ackermannviridae* as well as other unknown families, and *Ligamenvirales* order comprising *Lipothrixviridae* and ssDNA phage family *Microviridae*, whereas eukaryotic viruses are composed of *Papillomaviridae, Picornaviridae, Coronaviridae, Orthomyxoviridae* and *Anelloviridae* and *Virgaviridae* [31, 32]. Compared with healthy people, IBD patients have increased abundance of *Caudovirales*, *Lactococcus phages*, *Lactobacillus phages*, *Clostridium phages*, *Enterococcus phages* and *Streptococcus phages* [32]. After long-term receipt of immunosuppressive therapy, high levels of *Anelloviridae* were found in the stool of IBD patients [33]. In addition, human *papilloma virus* infection may also be a cause of IBD [34]. Moreover, there have been clues indicating an intimately interaction of viruses with other intestinal organisms [32, 35].

Roles of intestinal helminths in IBD

For millions of years, helminths have become an indispensable resident in the human gut. Among soil-transmitted helminths, the most common species that

can infect humans are said to be roundworms (*Ascaris lumbricoides*), whipworms (*Trichuris trichiura*) and hookworms (*Necator americanus* and *Ancylostoma duodenale*) [36]. Once intestinal helminths are eliminated, the incidence of IBD tends to increase and the intestinal inflammatory response is significantly reduced, suggesting that intestinal parasites may play a protective role in IBD. The hygiene hypothesis suggests that early childhood absent of exposure to commensal microbes and helminthic parasites increases susceptibility to IBD in their later life, which is very common in developed countries [37]. With expanding urbanization and increasing environment transition to a more hygienic state, the increase in IBD incidence appears to coincide with a decrease in the rate of helminth colonization in the host [37]. Compared to helminth-negative individuals, subjects colonized by helminths showed higher gut bacterial diversity in the Malaysian indigenous cohort [38]. Simultaneous differences in helminth prevalence and microbiome structure between rural and urban residents favor a link between helminth presence and bacterial microbiome structure, indicating a potential protective role of helminth against the IBD microbiome in rural residents [39].

Polymicrobial interactions in IBD

In local intestinal niche, the mutual interactions among bacteria, fungi, viruses and parasites might be a crucial stimulator to drive IBD. Generally, intestinal multi-microorganism interactions among these microbes are either beneficial or detrimental in the control of IBD. Some intestinal fungi can improve colitis by reducing bacterial virulence factors, and intestinal bacteria can also promote the colonization of beneficial fungi in intestinal tract to prevent colitis [30, 35]. While there are also several intestinal bacteria that are capable of assisting harmful fungi to aggravate colitis by producing fungal-modifying compounds and enzymes that can affect the fungal composition of the gut ecosystem [39]. Intestinal parasites can use immune tools to promote the colonization of protective gut bacteria, thereby lowering intestinal inflammation [40]. Viruses can inhibit the production of bacterial virulence factors to improve intestinal injury, indicating an antagonism between intestinal bacteria and viruses [35]. On the contrary, other viruses can aggravate IBD by being stably integrated into bacterial genome and increasing bacterial toxins [32].

Abnormal immune response to unbalanced gut flora in IBD

Intestinal flora imbalance finally interferes the functions of innate and/or acquired immunity to alleviate or worsen intestinal inflammation through activating B and/or T cells as well as producing a variety of cytokines (Table 1). The innate immune response can be initiated and strengthened by recognizing pathogen-associated molecular patterns (PAMPs) on dislodged organisms through types of pattern recognition receptors (PRRs) on innate cells including C-type lectin receptors, Toll-like receptors, nucleotide-binding oligomerization domain-like receptors and mannose receptors, followed by a cascade of signaling transductions [16, 18, 22, 24, 26, 30, 41–46]. Along with the activated innate immune response, the adaptive immune system is about to be highly motivated and take part in the modulation of IBD, and T subsets (Th1, Th2, Th17, Treg) are the most well-studied cells during the process of IBD [19, 23, 25, 39, 47–61].

MicroRNA and IBD

MicroRNA biology

The first microRNA (miRNA) was the heterogeneous gene lin-4 discovered from *Caenorhabditis elegans* in 1993 [62]. MiRNAs originate from DNA introns or exons which are transcribed by RNA polymerase II and III into a 1 kb long primary-miRNA with a hairpin-like structure. In the nucleus, the RNA-binding protein DGCR8 binds to the RNA-specific endoribonuclease (ribonuclease III) Drosha to form a microprocessor complex which cleaves primary miRNAs into precursor miRNAs containing stem-loop structures. Precursor miRNAs are exported into the cytoplasm by nuclear transporter exportin 5 and further cleaved by Dicer ribonuclease to remove the stem-loop, forming a miRNA duplex with approximately 22 nucleotides in length. These miRNA duplexes are loaded into the RNA-induced silencing complex (RISC), where Argonaute-2 (AGO2) and molecular chaperones such as HSC70 and HSP90 mediate the interaction of the miRNA's guide strand with its target mRNA, thereby inhibiting mRNA translation and/or increasing mRNA degradation (Fig. 1) [63]. According to the knowledge of the miRBase database, the number of known human microRNAs has been reached up to 2656 (see details at www.mirbase.org). A family of miRNAs with the same initial sequence can target a single gene, while in some cases, a single miRNA may affect dozens of genes [64]. Accumulating studies have shown that numerous miRNAs were differentially expressed in different cell types and tissues in mammals, mediating multiple cellular events including cell proliferation, differentiation, metabolism, apoptosis and development [64].

Table 1 Immunomodulatory effects of gut flora in IBD

Type of immunity	Gut flora	Abundance	Function	References
Innate immunity	*Ruminococcus gnavus*	Increased	Aggravating IBD by promoting tolerogenic immune response through the production of capsular polysaccharides	[41]
	Campylobacter concisus	Increased	Aggravating IBD by activating TLRs to increase the release of pro-inflammatory cytokines and intestinal permeability	[42]
	Salmonella Typhimurium	Increased	Activating NF-κB to regulate neutrophil migration to infectious focus	[43]
	Roseburia intestinalis	Decreased	Reducing inflammatory macrophages and Th17 cells in colon and down-regulating IL-6 and STAT3	[44]
	Candida albicans	Increased	Increasing intestinal inflammation by activating Dectin-1, TLR2 and TLR4 and their downstream effector NF-κB pathways	[22]
	Candida glabrata	Increased	Exacerbating colitis by triggering high expressions of TLR 4, 5, 8 and 9 and MBL-C	[18]
	Malassezia restricta elicits	Increased	Aggravating colitis through CARD9 mediated intestinal inflammation	[24]
	Trichosporon pullulans	Increased	Initiating a signaling cascade through TLR binding to phagocytes, leading to cellular activation and production of upregulated T-cell activity	[26]
	Saccharomyces boulardii	Decreased	Reducing the inflammatory response in IBD patients by regulating the secretion of anti-inflammatory factors	[30]
	Saccharomyces cerevisiae	Decreased	Alleviating IBD by inducing DC to exert anti-inflammatory effects	[16]
	Lactobacillus, Escherichia, Bacteroides bacteriophages	Increased	Exacerbating colitis via TLR9 and IFN-γ	[45]
	Murine norovirus	Increased	Exacerbating the disease course of IBD by enhancing DC antigen presentation	[46]
Adaptive immunity	*Segmented filamentous bacteria*	Increased	Exacerbating colitis by promoting the production of pathogenic Th17 cells	[47]
	Adherent-invasive E. coli	Increased	Increasing IL-1β production by inducing Th17 cells	[48]
	Bacteroides fragilis	Increased	Causing colitis by inducting Th17 to drive Stat3/IL-17	[49]
	Mycobacterium paratuberculosis	Increased	Exacerbating CD by proliferating T cells and increasing proinflammatory factors	[50]
	Clostridium difficile	Increased	Exacerbating IBD by regulating Th17 or Th1 cells to promote colon damage	[51]
	Faecalibacterium prausnitzii	Decreased	Ameliorating IBD by modulating Th17/Treg differentiation	[52]
	Lactobacillus reuteri	Decreased	Relieving intestinal inflammation of IBD by inducing $CD4^{+}CD8\alpha\alpha^{+}$ T cells in intestinal epithelium	[53]
	Bifidobacterium adolescentis	Decreased	Improving IBD by modulating Treg/Th2 responses	[54]
	Helicobacter pylori	Decreased	Preventing colitis by balancing Th17/Treg responses and shifting macrophages to an anti-inflammatory M2 phenotype	[55]
	Candida tropicalis	Increased	Accelerating colitis by inducing a strong Th1/Th17 response	[19]
	Cryptococcus neoformans	Increased	Inducing intestinal inflammation through γδT cells	[23]
	Aspergillus sydowii	Increased	Exacerbating IBD by driving Th1/Th2 combination to increase inflammation	[25]
	Cytomegalovirus	Increased	Increasing UC mucosal inflammation by promoting Th2 cytokines	[56]
	Epstein-Barr virus	Increased	Exacerbating IBD by increasing lymphoplasmacytic infiltration	[57]
	Schistosoma japonicum	Decreased	Relieving colitis by reducing Th1/Th2/Th17 response	[58]
	Trichinella spiralis	Decreased	Ameliorating UC by upregulation of TGF-β and IL-13	[59]
	Heligmosomoides polygyrus	Decreased	Blocking UC by downregulating Tregs to reduce Smad7 expression	[60]
	Trichuris muris	Decreased	Reducing intestinal inflammation by promoting the expansion of beneficial bacteria through type 2 immunity and inducing colonic inflammation by Th2-mediated response	[39, 61]

Roles of miRNAs in IBD

Inflammation

Excessive inflammation is a hallmark of inflamed colon tissue and blood in IBD hosts, and can be regulated by miRNAs in a direct or indirect way. As a whole, miRNAs can alter the production of local and/or systemic pro/anti-inflammatory factors to exasperate or improve IBD [65–68]. Since they have specific differential expressions in peripheral blood and colon tissues, a plenty of miRNAs are usually employed to differentiate UC and CD in clinical diagnosis [69]. The same miRNA may have diverse levels in different body parts, and the composition and concentration of miRNAs may also vary in different stages of IBD [69]. These variations suggest that miRNAs can present well-refined interconnection with inflammation in disordered IBD microenvironment.

Intestinal mucosal barrier

Intestinal mucosal barrier is an innate defense shield to prevent bacterial antigens and toxins from penetrating intestinal mucosa and plays a key role in maintaining intestinal homeostasis. One of IBD manifestations is the breakdown of intestinal mucosal barrier [70]. Many miRNAs are specific to affect intestinal mucosal structure and promote epithelial regeneration after injury [70, 71]. To keep intestinal mucosa intact, the tight junction (TJ) proteins ZO-1, Occludin and Claudin-1 can be rigorously modulated by miRNAs [72, 73]. For example, miR-155 and miR-223 could impair TJ proteins to promote intestinal epithelial damages [72, 73], while miR-21-5p, miR-423-5p, miR-320, and miR-126 appeared to protect or improve TJ barrier and intestinal permeability in IBD [74–77].

Autophagy

Autophagy is a process that depends on lysosomal pathway to degrade cytosolic proteins and organelles. In higher eukaryotes, autophagy is vital in cell differentiation, response to environmental stress and clearance of intracellular pathogenic microorganisms, etc. [78]. An autophagy process requires synergistic action of a variety of proteins, such as NOD2, IRGM, vimentin and multiprotein complexes (ATG16L1 and ATG5-ATG12) [78]. Many miRNAs can regulate these proteins, thereby controlling intestinal mucosal immunity and epithelial functions [68, 79, 80]. During the endoplasmic reticulum stress response, a group of miRNAs can utilize autophagy to regulate the unfolded protein response (UPR), a process that contributes to intestinal fibrosis in IBD [81]. There are also many miRNAs capable of inducing or inhibiting intestinal autophagy through mTOR signaling, thereby affecting inflammatory levels in IBD [77, 82].

Exosomes

Exosomes are membranous vesicles secreted by living cells with a diameter of 30–200 nm and are naturally present in body fluids such as blood, saliva, urine and breast milk [83]. Exosomes are a critical player in IBD development due to their wide-range capacity of a variety of functional molecules including especially miRNAs. For example, miR-223 is abundant in exosomes and can promote IBD through stimulating IL-32 inflammatory cascade [84]. Exosomal miRNAs can be transported among immune cells (DCs, T cells, macrophages, etc.) to regulate host immune defense to aberrant inflammations in IBD [85, 86]. Moreover, exosomal miRNAs can modulate gut barrier integrity and gut microbiota homeostasis to influence different stages of IBD [87].

Other small RNAs

Increasing evidence reveals that miRNAs can impose or be imposed on by other small RNAs including long non-coding RNAs (lncRNAs) and circular RNAs (circRNAs) during IBD pathogenesis. In some IBD patients, dysregulation of lncRNAs is thought to change intestinal mucosal functions through an interactive network among miRNAs, transcription factors and mRNAs [88]. Certain miRNA/lncRNA pairs have been identified as therapeutic targets for IBD patients [89]. CircRNAs can trigger a series of inflammatory events involved in IBD, and interact with miRNAs to affect the function of diverse immune cells (such as Tregs and DCs) in CD patients [90].

Disordered gut immune response to miRNA shifts

Incremental documents uncover the implications of innate and adaptive immune cells, including epithelial cells [71–77, 79, 80, 91–93], macrophage [68, 86, 94–109], neutrophil [110–113], NK cells [114], DCs [67, 115–122], Th17 cells [65, 123–129], Tregs [66, 130, 131] in IBD amelioration and exacerbation upon altered miRNA profiling (Table 2).

Complex interplay among miRNA, gut flora and immune system

There are complex interactions among miRNAs, gut flora and their secondary metabolites, as well as immune cells during IBD process. For instance, studies on miR-29, miR-10a, miR-34a, miR-135b, miR-21 and miR-107 demonstrated that these miRNAs acted as intermediates between *Enterobacteriaceae* and *Fusobacterium* and could exacerbate colitis by restricting

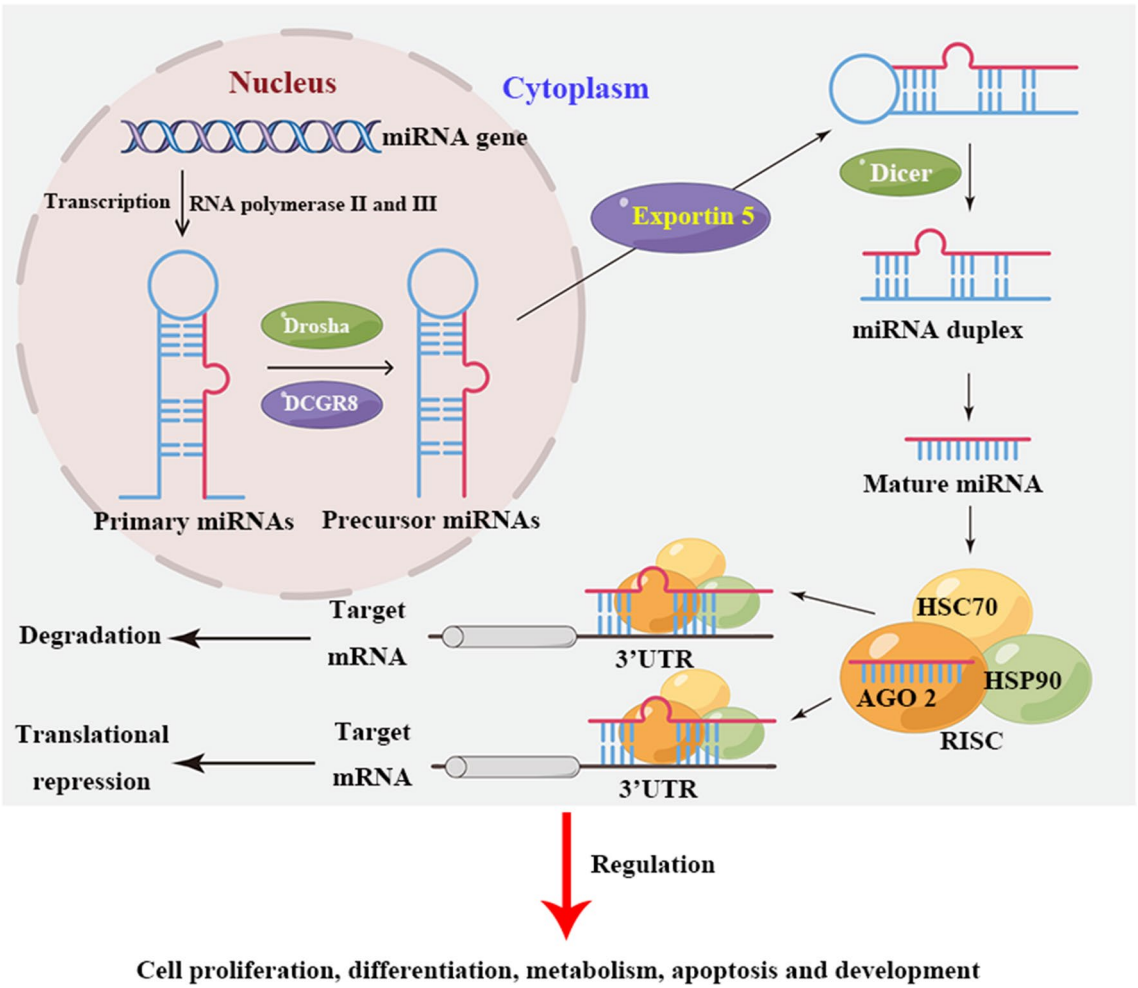

Fig. 1 Biosynthesis and function of miRNA

DCs and activating TLR-TLR ligand interactions [118, 132, 133]. Human leukocyte antigen (HLA) class I genes are the most polymorphic loci in human genome, resulting in HLA-I proteins capable of binding and presenting multiple antigenic peptides to cytotoxic T lymphocytes. This study further found that the subjects with HLA-C alleles regulated by miR-148a exhibited better HIV control but increased risk of CD [134]. Gut microbiota can protect intestinal integrity and alleviate intestinal inflammation by negatively regulating miR-10a expression in DCs and interacting with TLR signaling pathways [116]. Exosomal miRNAs derived from *Trichinella spiralis* muscle larvae can modulate T cell composition to alleviate colitis [135]. In addition, gut miRNAs are also involved in gut microbial disorders and subsequent immune responses [136]. Up till now, however, there have been no direct evidence to decipher the immunological mechanisms of mycobiota and miRNAs in IBD pathogenesis.

Immunotherapy of IBD

Targeting miRNA in IBD treatment

Since miRNAs are deeply involved in the regulation of microbiota and IBD progression, they may become promising targets for the treatment of IBD. At present, the immunomodulatory roles of specific miRNAs have been extensively elucidated in animal and human IBD models with bacterial dysbiosis, and miRNA-guided IBD treatment has shown to be clinically feasible and made great progress [71]. Because multiple genes may be simultaneously targeted by a single miRNA inhibitor or mimic, hidden danger to interfere the normal function of non-target genes may occasionally occur [137]. Therefore, exosomes and nanoparticles packaged with specific miRNAs have aroused extensive interests.

Exosomes are secreted by host body without immune rejection and can transport diverse cargos (e.g. miRNAs) to specific tissues [87, 98]. Recently, Gong et al. described

Table 2 Immunomodulatory effects of miRNA in the gut

Type of immunity	Immune cells	miRNAs	Function	References
Innate immunity`	Epithelial cells	miR-21-5p	Regulating intestinal epithelial permeability by ARF4 to control intestinal epithelial barrier function	[74]
		miR-155	Promoting intestinal barrier dysfunction through inhibiting the HIF-1α/TFF-3 axis	[72]
		miR-223	Disruption of intestinal barrier function by inhibiting CLDN8 of intestinal epithelial cells	[73]
		miR-423-5p	Relieving colitis by regulating NF-κB/MAPKs/JNK and IL-21/claudin-5 pathway	[75]
		miR-320a	Promoting barrier formation of human intestinal epithelial cells through hypoxia	[76]
		miR-126	Damaging intestinal mucosal barrier function through downregulating S1PR2 and preventing activation of PI3K/AKT signaling pathway	[77]
		miR-31	Alleviating colitis by reducing inflammatory signaling and promoting colonic epithelial cells	[71]
		miR-195-5p	Alleviating colitis by reducing intestinal permeability and promoting intestinal epithelial repair	[91]
		miR-301a	Promoting intestinal inflammation and aggravating colitis by inhibiting BTG1	[92]
		miR-142-3p	Targeting ATG16L1 to regulate autophagy to reduce intestinal inflammation in CD	[79]
		miR-196	Worsening CD by increasing AICE	[80]
		miR-200C-3p	Increasing TJ permeability by decreasing the expression of occludin	[93]
	Macrophage	miR-155, miR-155-5p	Inhibiting the proliferation of intestinal immune cells and the polarization of $CD4^+$ T cells to Th1 and Th17 by M2 macrophages	[94, 95]
		miR-433-3p	Inhibiting MAPK signaling pathway and reducing the production of inflammatory cytokines	[96]
		miR-494-3p	Ameliorating colitis by targeting IKKβ/NF-κB to inhibit macrophage recruitment, M1 activation and EDA-A2 secretion	[97]
		miR-378a-5p, miR-223	Inhibiting NLRP3 inflammasome to eliminate macrophage pyroptosis	[98, 99]
		miR-125b	Promoting polarization of M1 to M2 macrophage	[100]
		miR-148a	Inhibiting upstream regulators of NF-κB and STAT3 signaling	[101]
		miR-182-5p, miR-145-5p, miR-200b-5p, miR-217-5p, miR-146a-5p	Downregulating inflammatory markers to improve colitis	[102]
		miR-590-3p	Attenuating mucosal injury and promoting epithelial repair through LATS1/YAP/ β-catenin signal axis	[103]
		miR-146a	Coordinating inflammatory responses by activating NOD2-SHH signaling in a colitis model	[104]
		miR-21	Exacerbating colitis by increasing TNF-α and macrophage inflammatory protein-2 level	[105]
		miR-497	Inhibiting colitis through Wnt/β-catenin pathway	[106]
		miR-466i, miR-140-5p, miR-301b-3p	Being involved in immune responses to *C. albicans* via TGF-β and regulating MAPK pathway	[107]
		miR-342-3p	Promoting inflammatory responses in macrophages infected with *Trichosporon asahii* by negatively regulating Dectin-1 to promote the expressions of TNF-α and IL-6	[108]

Table 2 (continued)

Type of immunity	Immune cells	miRNAs	Function	References
		miR-374a-5p	Exacerbating IBD by increasing pro-inflammatory mediators to control macrophage-driven inflammation	[109]
		miR-122	Targeting NOD2 to reduce intestinal epithelial cell damage in CD	[68]
		miR-148b-5p	Promoting the repair of colon tissue damage in IBD by down-regulating 15-lox-1 in macrophages	[86]
	Neutrophil	miR-146a	Relieving colitis by reducing neutrophils in the gut	[110]
		miR-23a/miR-155	Exacerbating IBD through inducing DSB accumulation and delaying wound healing	[111, 112]
		miR-223	Alleviating experimental colitis by reducing NLRP3 levels and IL-1β release	[113]
	NK	miR-17/20a	Targeting MEKK2 to enhance the anti-tumor activity of NK cells	[114]
	DC	miR-3909, miR-130a-3p	Reducing intestinal inflammation by inhibiting TNF signaling	[115]
		miR-10a	Inhibiting NOD2 and IL-12/IL-23p40 in inflamed mucosa	[116]
		miR-29	Mitigating IBD by targeting $CD11c^+$ DCs or limiting IL-23 release	[117, 118]
		miR-369-3p	Reducing intestinal inflammation and alleviating colitis by inhibiting DC and promoting the secretion of anti-inflammatory factors	[67]
		miR-181a	Modulating ERK-MAPK signaling and maintaining DCs-SIGN expression in UC mice	[119]
		miR-107	Improving UC by inhibiting IL-23p19 expression and maintaining intestinal homeostasis	[120]
		miR-223	Reducing intestinal inflammation by targeting C/EBPβ to regulate intestinal DCs	[121]
		miR-144/451	Relieving colitis by targeting interferon regulatory factor 5 and reducing DC activity	[122]
Adaptive immunity	Th17	miR-219a-5p	Suppressing intestinal inflammation by inhibiting Th1/Th17 mediated immune responses	[123]
		miR-425	Aggravating IBD by downregulating Foxo1-mediated generation of diseased Th17 cells	[124]
		miR-155	Aggravating IBD by promoting Th17 cell differentiation and increasing Th1/17 response	[125, 126]
		miR-31	Relieving CD by restoring IL-25 expression in colon and blocking Th17 response	[127]
		miR-301a	Promoting intestinal mucosal inflammation by inducing IL-17A and TNF-a	[65]
		miR-125a, miR-125b	Relieving colitis by inhibiting Th17 cell differentiation	[128]
		miR-212/132	Aggravating IBD by increasing Th17 cell levels and decreasing elevated levels of IL-10-producing $CD4^+$ cells	[129]
	Treg	miR-106a	Post-transcriptional regulation of IL-10 release	[66]
		miR-155	Aggravating IBD by targeting CTLA-4 expression in cTregs and Tfr and promoting germinal center (GC) B cell activation and autoantibody overproduction	[130]
		miR-125a	Ameliorating IBD by modulating the function of Tregs through IL-6-STAT3 signaling pathway	[131]

a potential contributor of let-7b-5p/TLR-4 pathway in macrophage activation and inflammatory response, and further demonstrated a prominent colitis alleviation achieved by serum exosome mediated let-7b-5p mimic delivery [138]. Exosomal transportation systems can prevent the transported miRNAs from degradation, and become an important tool to promote the development of personalized medicines [138]. However, exosome therapy for IBD is still in the early stage and far from clinical purpose. The ideal exosome bionics should possess the advantages of high carrying capacity, strong versatility, non-toxicity, easy modification and administration [139]. In addition, there are still several problems including the mechanistic relationship between exosomes and IBD development, the improvement of exosome drug delivery methods and targeted modification technology, exosome production and purification that have to be addressed prior to clinical applications [139].

Nano-delivery system is another hopeful approach for IBD treatment. Nanoparticles have a wide size range from a few nanometers to 1000 nm. After oral or intravenous administration, the drug can quickly reach and remain in the colon for a relatively long time, which is beneficial for local therapy. Current nanoparticle mediated miRNA delivery systems (< 1 μm diameter) comprise lipid-based systems, polyethylenimine (PEI) based systems, dendrimers and polylactide-coglycolide (PLGA) particles, natural polymers (chitosan, protamine, atelocollagen), and inorganic materials such as functionalized gold and silica [117]. Viola Neudecker et al. [113] observed an attenuated experimental colitis by nanoparticle-mediated overexpression of miR-223. MiR-29 and supercarbonate apatite (sCA) nanoparticles were formerly used as a drug delivery system to improve colitis in mice by intravenous injection of sCA-miR-29a-3p or sCA-miR-29b-3p targeting DCs in the inflamed colon [117]. Encapsulation of miR-31 mimetic particles into oxidized konjac glucomannan (OKGM) microspheres was demonstrated to capably ameliorate DSS-induced colitis in mice [71]. Although nanoparticles have the advantage of particle size and can preferentially accumulate in inflammatory areas, the toxicity of nanoparticles has not yet been fundamentally solved [140]. Since physiological status changes from time to time in gastrointestinal tract, the structural stability of drug delivery system during gastrointestinal transport needs to be further optimized to prevent premature release in the stomach and small intestine [140]. Meanwhile, many drug delivery systems are still at in vitro research stage, and the interaction between nano/micron particles and human organs/tissues are also waiting for further elucidation [140].

Targeting gut microbiota in IBD treatment

Antibiotics can alleviate IBD by altering the abundance and diversity of intestinal flora, including increasing the proportion of beneficial bacteria, reducing bacterial invasion into surrounding tissues and micro-abscess formation, blocking bacterial translocation, etc. [141]. It has been reported that quinolones and nitroimidazole had certain curative effects on CD, and ciprofloxacin and metronidazole were effective in treating CD complicated by perianal lesions and fistula [141]. However, long-term use of antibiotics not only compromises host immunity, but also induces several irreversible defects such as serious adverse reactions and easy recurrence after drug withdrawal [141]. Notably, there are a few studies on the application of antibiotics for UC treatment at present. Since intestinal fungi can aggravate IBD, it is sensible to assume that strategies targeting intestinal fungi are likely to be effective for IBD therapy. Thus, antifungal agents appear to be a potential approach in the treatment of IBD with fungal dysbiosis. Commercial antifungals for clinical purpose consist of azoles, echinocandins, polyenes and flucytosine with varying mechanisms acting on different fungal cell structures [142]. There are also increasing evidence showing that many local traditional medicines contain abundant active compounds with antimicrobial functions [22]. Due to rising emergence of drug resistance and limited antimicrobial agents in hand, combinatory strategy has been employed to decrease or reverse resistance of clinical strains to conventional antimicrobial drugs [141, 142]. Meantime, the advancement of biomaterial science paves a way for use of nano-drugs in the antimicrobial field. The physicochemical and biological properties of nano-drugs can reduce their toxic and side effects, improve their stability and bioavailability, and selectively target tissues and cells by structural modification, thereby improving their antimicrobial effects [140]. However, a key deficiency of nano-drugs for antimicrobial purpose is their relatively poor immediate effect [140]. Moreover, antimicrobial drugs can influence most of the intestinal flora with a consequence that both harmful and beneficial microorganisms are all inhibited, resulting in intestinal flora imbalance and subsequent mucosal immune disorders [141].

Microbiological therapies, mainly including probiotics and fecal microbiota transplantation (FMT), have been widely used to prevent IBD. Probiotics are a class of living microorganisms with beneficial effects on the body by reducing epithelial cell apoptosis and intestinal mucosal inflammation when consumed in sufficient doses [30]. There are a bunch of successful application of probiotics for IBD treatment through maintaining intestinal microecological equilibrium. For example, *S. boulardii*, the only probiotic yeast commercially available, can reduce inflammation and *C. albicans* colonization in a mouse colitis

model [30]. *L. rhamnosus* L34 ameliorates the severity of mice colitis by reducing intestinal fungi and fecal dysbiosis [143]. At present, the clinical probiotic preparations mainly include oral liquid, fermented milk freeze-dried powder, bacterial powder capsules, microcapsules, etc. It could be expected that the use of probiotics can achieve satisfactory results for IBD therapy after sufficient rigorous clinical trials can provide solid evidence of its clinical safety and efficiency. FMT is a purposed method for intestinal disorders and usually performed by preparing stool suspension from healthy donors with dilution, homogenization, filtration and finally mixing with normal saline and glycerin [144]. Family members or friends and healthy volunteers are all suitable donors [144]. FMT was for the first time adopted in a patient with refractory UC who had improved conditions under endoscope with no symptoms during the 6-month follow-up after 3 months of treatment [145]. However, the clinical samples receiving FMT are still relatively small, and the clinical effectiveness is mainly evaluated by the relief of symptoms, which may be affected by many factors including donor screening, preparation of fecal bacterial fluid, transplantation route and frequency, severity of patient's condition and so on [145]. As a result, the objectivity and reliability of FMT results are generally poor.

Other immunomodulatory approach for IBD treatment

Some scholars have found that TNF-α can be detected in 40 to 45% of active IBD patient serum, but rarely in healthy individuals. As a result, blocking the pathway for the production, regulation and action of TNF-α can achieve the purpose of controlling inflammation and continuously relieving the disease. Besides glucocorticoids, anti-TNF-α monoclonal antibodies have been demonstrated to have a good therapeutic effect [146]. Infliximab is a mouse-human chimera TNF-α monoclonal IgG antibody and can effectively and quickly neutralize TNF-α. Bortlik et al. [147]d believed that infliximab reaching a plasma concentration of 3 μg/mL before maintenance therapy (some studies set this threshold as 2 μg/mL) could help maintain remission in CD patients. Golimumab is an anti-TNF drug used to treat moderately to severely active UC. Subcutaneous administration of golimumab at 200 mg and 400 mg alleviates clinical response, promotes mucosal healing, and improves quality of life in active UC patients [148]. However, approximately 40% of patients who initially respond to anti-TNF-α therapy subsequently lose this response, requiring dose ascending or drug switching [149]. Furthermore, long-term use of anti-TNF-α antibodies has been regarded as a predisposing factor for treatment failure [149]. It needs to note that there are a series of adverse reactions of anti-TNF-α antibodies mainly comprising infection, infusion reaction, delayed-type allergic reaction, autoantibody and drug-induced lupus erythematosus, central nervous system demyelinating disease, aggravated moderate or more congestive heart failure, high risk of lymphoma or malignancy [149].

Perspectives

Here the immunomodulatory roles of gut flora and miRNAs have been comprehensively reviewed based on recent publications (Fig. 2). Although it is obscure to illuminate their cause and effect in IBD pathogenesis, further efforts on deciphering the immune-regulatory mechanisms of gut flora and miRNAs are warranted. For example, as an important intestinal opportunistic fungus, there is still much lack of knowledge on the contribution of *C. albicans* to the progression of IBD and the underlying mechanisms by which innate and adaptive immune responses to overcolonized *C. albicans* occur in the gut. According to an unpublished report, we found that several miRNAs, previously not implicated in IBD, were differentially expressed in a colitis model with *C. albicans* interference. These results may guide scientific attention to the role of specific miRNAs in IBD settings with mycobiota dysbiosis. Nevertheless, as far as clinical application, there are still several concerns that may be well deserved for future efforts.

1. At the moment of pandemic of COVID-19, it has an emergent requisite to monitor the alterations of gut flora, miRNAs and immune system in IBD patients. It was reported that UC might be a sequelae after COVID-19 infection, and IBD individuals might be particularly susceptible to COVID-19 that can cause progressive pneumonia, acute respiratory distress syndrome and organ failure driven by abnormal immune reactions including hyper-inflammation and a cytokine storm syndrome [150, 151]. Accumulating evidence shows that compared to the healthy people, the patients infected with SARS-CoV-2 are mainly characterized by the depletion of *Aspergillus* and *Penicillium* with higher fungal burden and have significant alterations in the fecal mycobiomes with enriched *C. albicans* in the gut [152, 153].
2. Although the main damages of IBD are restricted in the gut, the diversity and abundance of gut flora and miRNA profiling are definitely interconnected among organs and/or tissues through certain axis. Indeed, there have been increasing documents to describe how these axis including brain-gut axis, liver-gut axis, lung-gut axis perform and function [154–156]. The in-depth knowledge of these interconnected axis can greatly widen and expand our views on the occurrence, development and prevention of IBD.

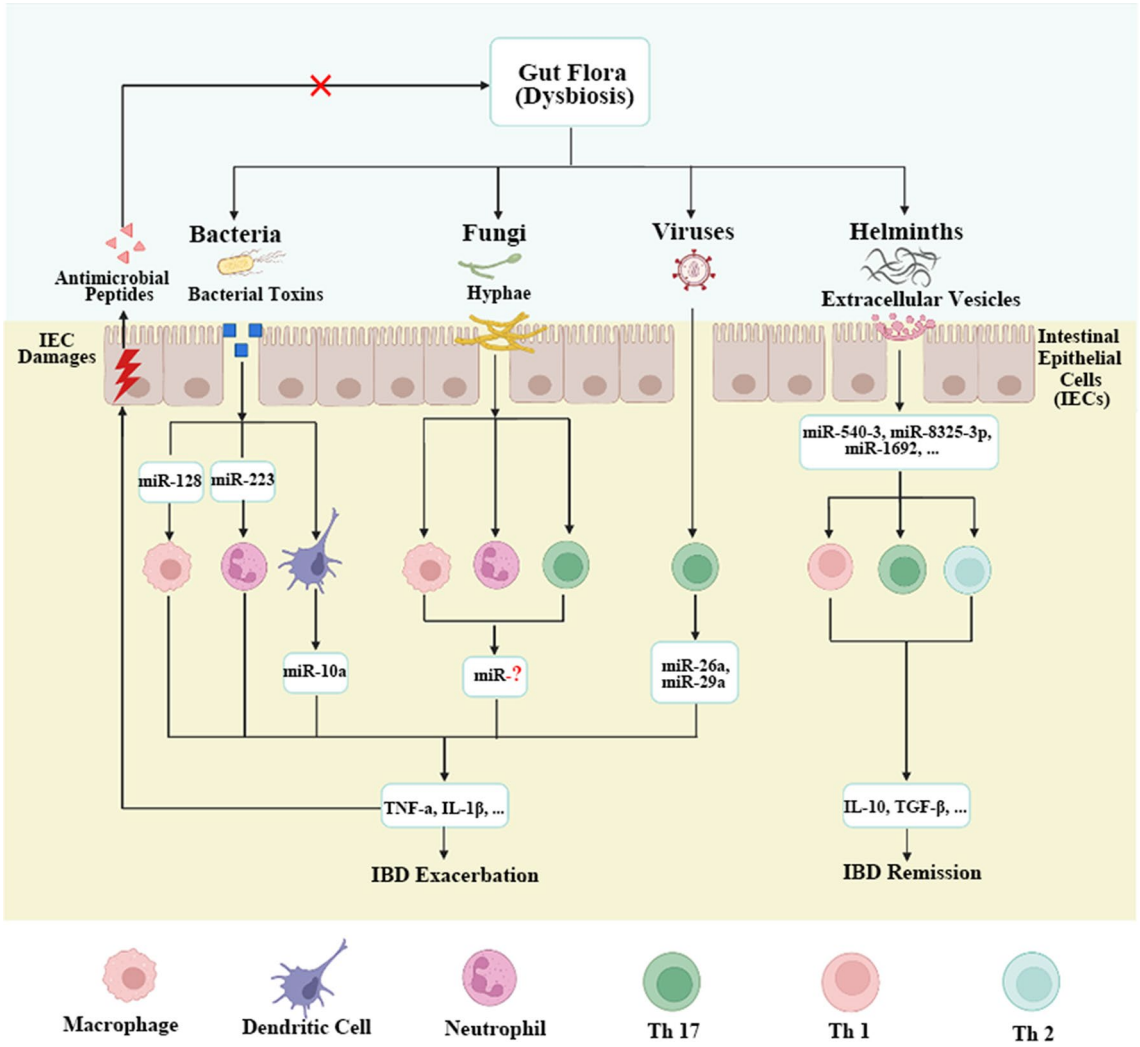

Fig. 2 Immuno-interaction between gut flora and intestinal mucosa with an involvement of miRNAs as a fine-tuned mediator. The gut flora is mainly composed of bacteria, fungi, viruses, and helminths. Bacteria can secrete bacterial toxins and modulate the activities of macrophages and neutrophils by miR-128 and miR-223. These virulence factors can also regulate miR-10a to restrict the activity of dendritic cells (DCs), consequently aggravating intestinal inflammation and intestinal epithelial cells (IECs) damage. Fungi can form hyphae to enhance the colonization of intestinal mucosa and activate macrophage, DCs and neutrophil, damaging mucosal barrier integrity and aggravating intestinal inflammation. During viral infection, reduced miR-26a and miR-29a in colonic mucosa activate Th17 to cause chronic active inflammation and IEC damage. Helminths are a group of intestinal worms and can secrete membrane-bound structures called extracellular vesicles (EVs) which contain multiple miRNAs. These miRNAs can inhibit intestinal inflammation with incremental anti-inflammatory factors (IL-10, TGF-β, etc.) and intestinal damage with reduced Th1 and Th17 and increased Th2. Although the dysbiosis caused by bacteria, fungi and viruses usually stimulates elevation of inflammation, the damaged IEC by pro-inflammatory factors (TNF-α, IL-1β, etc.) can generate a variety of antimicrobial peptides that are capable of inhibiting overgrown microorganisms, so as to realize the multi-level "management" of gut flora and maintain gut flora homeostasis

3. Since it has been put forward, precision medicine has received great achievements in IBD therapy. Many drugs and traumatic surgical approaches are extraordinarily effective at the beginning phase of IBD. However, multiple pathogenic stimuli usually make IBD remission become tough. In view of this intractability, alternative and complementary therapies are urgently required besides precision medicine for IBD treatment. Traditional Chinese Medicine (TCM) has accumulated abundant experience in the treatment of IBD since the first description of colitis was recorded in the renown medical literature *HuangDi NeiJing* with over 4000 years old [157]. TCM deems the body as a whole and emphasizes recuperation during the remission of IBD using diverse traditional formulae and decoctions which usually have multiple functions contributory for recovery. Since these formulae and decoctions have complex components, however, more efforts should be performed on the qual-

ity control and deciphering the underlying pharmacological mechanisms.

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Declarations

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References

1. Kaplan GG, Windsor JW. The four epidemiological stages in the global evolution of inflammatory bowel disease. Nat Rev Gastroenterol Hepatol. 2021;18:56–66. https://doi.org/10.1038/s41575-020-00360-x.
2. Feuerstein JD, Cheifetz AS. Crohn disease: epidemiology, diagnosis, and management. Mayo Clin Proc. 2017;92:1088–103. https://doi.org/10.1016/j.mayocp.2017.04.010.
3. Sýkora J, Pomahačová R, Kreslová M, et al. Current global trends in the incidence of pediatric-onset inflammatory bowel disease. World J Gastroenterol. 2018;24:2741–63. https://doi.org/10.3748/wjg.v24.i25.2741.
4. Feuerstein JD, Moss AC, Farraye FA. Ulcerative colitis. Mayo Clin Proc. 2019;94:1357–73. https://doi.org/10.1016/j.mayocp.2019.01.018.
5. Da Silva BC, Lyra AC, Rocha R, et al. Epidemiology, demographic characteristics and prognostic predictors of ulcerative colitis. World J Gastroenterol. 2014;20:9458–67. https://doi.org/10.3748/wjg.v20.i28.9458.
6. Hallen-Adams HE, Suhr MJ. Fungi in the healthy human gastrointestinal tract. Virulence. 2017;8:352–8. https://doi.org/10.1080/21505594.2016.1247140.
7. Putignani L, Oliva S, Isoldi S, et al. Fecal and mucosal microbiota profiling in pediatric inflammatory bowel diseases. Eur J Gastroenterol Hepatol. 2021;33:1376–86. https://doi.org/10.1097/meg.0000000000002050.
8. Conte MP, Aleandri M, Marazzato M, et al. The adherent/invasive *Escherichia coli* strain LF82 invades and persists in human prostate cell line RWPE-1, activating a strong inflammatory response. Infect Immun. 2016;84:3105–13. https://doi.org/10.1128/iai.00438-16.
9. Lee CG, Hwang S, Gwon SY, et al. *Bacteroides fragilis* toxin induces intestinal epithelial cell secretion of interleukin-8 by the E-cadherin/β-catenin/NF-κB dependent pathway. Biomedicines. 2022;10:827. https://doi.org/10.3390/biomedicines10040827.
10. Hoter A, Naim HY. The Functions and therapeutic potential of heat shock proteins in inflammatory bowel disease-an update. Int J Mol Sci. 2019;20:5331. https://doi.org/10.3390/ijms20215331.
11. Zhang P, Minardi LM, Kuenstner JT, et al. Serological testing for *Mycobacterial* heat shock protein HSP65 antibody in health and diseases. Microorganisms. 2019;8:47. https://doi.org/10.3390/microorganisms8010047.
12. Srivastava A, Gupta J, Kumar S, et al. Gut biofilm forming bacteria in inflammatory bowel disease. Microb Pathog. 2017;112:5–14. https://doi.org/10.1016/j.micpath.2017.09.041.
13. Parada Venegas D, De La Fuente MK, Landskron G, et al. Short chain fatty acids (SCFAs)-mediated gut epithelial and immune regulation and its relevance for inflammatory bowel diseases. Front Immunol. 2019;10:277. https://doi.org/10.3389/fimmu.2019.00277.
14. Halder V, Porter CBM, Chavez A, et al. Design, execution, and analysis of CRISPR-Cas9-based deletions and genetic interaction networks in the fungal pathogen *Candida albicans*. Nat Protoc. 2019;14:955–75. https://doi.org/10.1038/s41596-018-0122-6.
15. Corvilain E, Casanova JL, Puel A. Inherited CARD9 deficiency: invasive disease caused by *Ascomycete* fungi in previously healthy children and adults. J Clin Immunol. 2018;38:656–93. https://doi.org/10.1007/s10875-018-0539-2.
16. Sokol H, Leducq V, Aschard H, et al. Fungal microbiota dysbiosis in IBD. Gut. 2017;66:1039–48. https://doi.org/10.1136/gutjnl-2015-310746.
17. Li J, Chen D, Yu B, et al. Fungi in gastrointestinal tracts of human and mice: from community to functions. Microb Ecol. 2018;75:821–9. https://doi.org/10.1007/s00248-017-1105-9.
18. Charlet R, Bortolus C, Sendid B, et al. *Bacteroides thetaiotaomicron* and *Lactobacillus johnsonii* modulate intestinal inflammation and eliminate fungi via enzymatic hydrolysis of the fungal cell wall. Sci Rep. 2020;10:11510. https://doi.org/10.1038/s41598-020-68214-9.
19. Di Martino L, De Salvo C, Buela KA, et al. *Candida tropicalis* infection modulates the gut microbiome and confers enhanced susceptibility to colitis in mice. Cell Mol Gastroenterol Hepatol. 2022;13:901–23. https://doi.org/10.1016/j.jcmgh.2021.11.008.
20. Li XV, Leonardi I, Putzel GG, et al. Immune regulation by fungal strain diversity in inflammatory bowel disease. Nature. 2022;603:672–8. https://doi.org/10.1038/s41586-022-04502-w.
21. Mao X, Ma J, Jiao C, et al. *Faecalibacterium prausnitzii* attenuates DSS-induced colitis by inhibiting the colonization and pathogenicity of *Candida albicans*. Mol Nutr Food Res. 2021;65:e2100433. https://doi.org/10.1002/mnfr.202100433.
22. Ge Y, Pan M, Zhang C, et al. Paeonol alleviates dextran sodium sulfate induced colitis involving *Candida albicans*-associated dysbiosis. Med Mycol. 2021;59:335–44. https://doi.org/10.1093/mmy/myaa053.
23. Sciaudone G, Pellino G, Guadagni I, et al. Disseminated *Cryptococcus neoformans* infection and Crohn's disease in an immunocompetent patient. J Crohns Colitis. 2011;5:60–3. https://doi.org/10.1016/j.crohns.2010.08.003.
24. Limon JJ, Tang J, Li D, et al. *Malassezia* is associated with Crohn's disease and exacerbates colitis in mouse models. Cell Host Microbe. 2019;25:377-88.e6. https://doi.org/10.1016/j.chom.2019.01.007.
25. Rodriguez-Palacios A, Aladyshkina N, Retuerto M, et al. Clinical effects of gamma-radiation-resistant *Aspergillus sydowii* on germ-free mice immunologically prone to inflammatory bowel disease. J Pathog. 2016;2016:5748745. https://doi.org/10.1155/2016/5748745.
26. Lestini BJ, Church JA. *Trichosporon pullulans* as a complication of chronic granulomatous disease in a patient undergoing immunosuppressive therapy for inflammatory bowel disease. Pediatr

Infect Dis J. 2006;25:87–9. https://doi.org/10.1097/01.inf.0000195641.69380.a0.
27. Wang Y, Wear M, Kohli G, et al. Inositol metabolism regulates capsule structure and virulence in the human pathogen *Cryptococcus neoformans*. mBio. 2021;12:e0279021. https://doi.org/10.1128/mBio.02790-21.
28. Bossou YM, Serssar Y, Allou A, et al. Impact of mycotoxins secreted by *Aspergillus* molds on the inflammatory response of human corneal epithelial cells. Toxins (Basel). 2017;9:197. https://doi.org/10.3390/toxins9070197.
29. Le Han H, Jiang L, Thu Tran TN, et al. Whole-genome analysis and secondary metabolites production of a new strain *Brevibacillus halotolerans* 7WMA2: a potential biocontrol agent against fungal pathogens. Chemosphere. 2022;307:136004. https://doi.org/10.1016/j.chemosphere.2022.136004.
30. Kunyeit L, KA AA, Rao RP. Application of probiotic yeasts on *Candida* species associated infection. J Fungi (Basel). 2020;6:189. https://doi.org/10.3390/jof6040189.
31. Adiliaghdam F, Amatullah H, Digumarthi S, et al. Human enteric viruses autonomously shape inflammatory bowel disease phenotype through divergent innate immunomodulation. Sci Immunol. 2022;7:6660. https://doi.org/10.1126/sciimmunol.abn6660.
32. Imai T, Inoue R, Nishida A, et al. Features of the gut prokaryotic virome of Japanese patients with Crohn's disease. J Gastroenterol. 2022;57:559–70. https://doi.org/10.1007/s00535-022-01882-8.
33. Liang G, Conrad MA, Kelsen JR, et al. Dynamics of the stool virome in very early-onset inflammatory bowel disease. J Crohns Colitis. 2020;14:1600–10. https://doi.org/10.1093/ecco-jcc/jjaa094.
34. Segal JP, Askari A, Clark SK, et al. The incidence and prevalence of human papilloma virus-associated cancers in IBD. Inflamm Bowel Dis. 2021;27:34–9. https://doi.org/10.1093/ibd/izaa035.
35. Sovran B, Planchais J, Jegou S, et al. *Enterobacteriaceae* are essential for the modulation of colitis severity by fungi. Microbiome. 2018;6:152. https://doi.org/10.1186/s40168-018-0538-9.
36. Panelli S, Epis S, Cococcioni L, et al. Inflammatory bowel diseases, the hygiene hypothesis and the other side of the microbiota: parasites and fungi. Pharmacol Res. 2020;159:104962. https://doi.org/10.1016/j.phrs.2020.104962.
37. Finlay CM, Walsh KP, Mills KH. Induction of regulatory cells by helminth parasites: exploitation for the treatment of inflammatory diseases. Immunol Rev. 2014;259:206–30. https://doi.org/10.1111/imr.12164.
38. Loke P, Lee SC, Oyesola OO. Effects of helminths on the human immune response and the microbiome. Mucosal Immunol. 2022. https://doi.org/10.1038/s41385-022-00532-9.
39. Ramanan D, Bowcutt R, Lee SC, et al. Helminth infection promotes colonization resistance via type 2 immunity. Science. 2016;352:608–12. https://doi.org/10.1126/science.aaf3229.
40. Kernbauer E, Ding Y, Cadwell K. An enteric virus can replace the beneficial function of commensal bacteria. Nature. 2014;516:94–8. https://doi.org/10.1038/nature13960.
41. Henke MT, Brown EM, Cassilly CD, et al. *Capsular polysaccharide* correlates with immune response to the human gut microbe *Ruminococcus gnavus*. Proc Natl Acad Sci U S A. 2021;118:e2007595118. https://doi.org/10.1073/pnas.2007595118.
42. Liu F, Ma R, Wang Y, et al. The clinical importance of *Campylobacter concisus* and other human hosted *Campylobacter* species. Front Cell Infect Microbiol. 2018;8:243. https://doi.org/10.3389/fcimb.2018.00243.
43. Schultz BM, Paduro CA, Salazar GA, et al. A potential role of *Salmonella* infection in the onset of inflammatory bowel diseases. Front Immunol. 2017;8:191. https://doi.org/10.3389/fimmu.2017.00191.
44. Nie K, Ma K, Luo W, et al. *Roseburia intestinalis*: a beneficial gut organism from the discoveries in genus and species. Front Cell Infect Microbiol. 2021;11:757718. https://doi.org/10.3389/fcimb.2021.757718.
45. Ungaro F, Massimino L, D'alessio S, et al. The gut virome in inflammatory bowel disease pathogenesis: from metagenomics to novel therapeutic approaches. United European Gastroenterol J. 2019;7:999–1007. https://doi.org/10.1177/2050640619876787.
46. Tarris G, De Rougemont A, Charkaoui M, et al. Enteric viruses and inflammatory bowel disease. Viruses. 2021;13:104. https://doi.org/10.3390/v13010104.
47. Lee JY, Hall JA, Kroehling L, et al. Serum amyloid a proteins induce pathogenic th17 cells and promote inflammatory disease. Cell. 2020;183:2036–9. https://doi.org/10.1016/j.cell.2020.12.008.
48. Viladomiu M, Metz ML, Lima SF, et al. Adherent-invasive *E. coli* metabolism of propanediol in Crohn's disease regulates phagocytes to drive intestinal inflammation. Cell Host Microbe. 2021;29:607–19. https://doi.org/10.1016/j.chom.2021.01.002.
49. Zamani S, Hesam Shariati S, Zali MR, et al. Detection of enterotoxigenic *Bacteroides fragilis* in patients with ulcerative colitis. Gut Pathog. 2017;9:53. https://doi.org/10.1186/s13099-017-0202-0.
50. Sibartie S, Scully P, Keohane J, et al. *Mycobacterium avium subsp. Paratuberculosis* (MAP) as a modifying factor in Crohn's disease. Inflamm Bowel Dis. 2010;16:296–304. https://doi.org/10.1002/ibd.21052.
51. Yu H, Chen K, Sun Y, et al. Cytokines are markers of the *Clostridium difficile*-induced inflammatory response and predict disease severity. Clin Vaccine Immunol. 2017;24:e00037-e117. https://doi.org/10.1128/cvi.00037-17.
52. Zhou L, Zhang M, Wang Y, et al. *Faecalibacterium prausnitzii* produces butyrate to maintain Th17/Treg balance and to ameliorate colorectal colitis by inhibiting histone deacetylase 1. Inflamm Bowel Dis. 2018;24:1926–40. https://doi.org/10.1093/ibd/izy182.
53. Cervantes-Barragan L, Chai JN, Tianero MD, et al. *Lactobacillus reuteri* induces gut intraepithelial $CD4^+CD8\alpha\alpha^+$ T cells. Science. 2017;357:806–10. https://doi.org/10.1126/science.aah5825.
54. Fan L, Qi Y, Qu S, et al. *B. adolescentis* ameliorates chronic colitis by regulating Treg/Th2 response and gut microbiota remodeling. Gut Microbes. 2021;13:1–17. https://doi.org/10.1080/19490976.2020.1826746.
55. Zhang H, Dai Y, Liu Y, et al. *Helicobacter pylori* colonization protects against chronic experimental colitis by regulating Th17/Treg balance. Inflamm Bowel Dis. 2018;24:1481–92. https://doi.org/10.1093/ibd/izy107.
56. Jentzer A, Veyrard P, Roblin X, et al. Cytomegalovirus and inflammatory bowel diseases (IBD) with a special focus on the link with ulcerative colitis (UC). Microorganisms. 2020;8:1078. https://doi.org/10.3390/microorganisms8071078.
57. Nissen LH, Nagtegaal ID, De Jong DJ, et al. *Epstein-Barr virus* in inflammatory bowel disease: the spectrum of intestinal lymphoproliferative disorders. J Crohns Colitis. 2015;9:398–403. https://doi.org/10.1093/ecco-jcc/jjv040.
58. Liu Y, Ye Q, Liu YL, et al. *Schistosoma japonicum* attenuates dextran sodium sulfate-induced colitis in mice via reduction of endoplasmic reticulum stress. World J Gastroenterol. 2017;23:5700–12. https://doi.org/10.3748/wjg.v23.i31.5700.
59. Pang J, Ding J, Zhang L, et al. Effect of recombinant serine protease from adult stage of *Trichinella spiralis* on TNBS-induced experimental colitis in mice. Int Immunopharmacol. 2020;86:106699. https://doi.org/10.1016/j.intimp.2020.106699.

60. Hang L, Kumar S, Blum AM, et al. *Heligmosomoides polygyrus bakeri* infection decreases smad7 expression in Intestinal CD4(+) T cells, which allows TGF-β to induce IL-10-producing regulatory T cells that block colitis. J Immunol. 2019;202:2473–81. https://doi.org/10.4049/jimmunol.1801392.
61. Scott NA, Andrusaite A, Andersen P, et al. Antibiotics induce sustained dysregulation of intestinal T cell immunity by perturbing macrophage homeostasis. Sci Transl Med. 2018;10:eaao4755. https://doi.org/10.1126/scitranslmed.aao4755.
62. Aziz F, Chakraborty A, Khan I, et al. Relevance of miR-223 as potential diagnostic and prognostic markers in cancer. Biology (Basel). 2022;11:249. https://doi.org/10.3390/biology11020249.
63. Mori MA, Ludwig RG, Garcia-Martin R, et al. Extracellular miRNAs: from biomarkers to mediators of physiology and disease. Cell Metab. 2019;30:656–73. https://doi.org/10.1016/j.cmet.2019.07.011.
64. Kabekkodu SP, Shukla V, Varghese VK, et al. Clustered miRNAs and their role in biological functions and diseases. Biol Rev Camb Philos Soc. 2018;93:1955–86. https://doi.org/10.1111/brv.12428.
65. He C, Shi Y, Wu R, et al. MiR-301a promotes intestinal mucosal inflammation through induction of IL-17a and TNF-α in IBD. Gut. 2016;65:1938–50. https://doi.org/10.1136/gutjnl-2015-309389.
66. Sanctuary MR, Huang RH, Jones AA, et al. MiR-106a deficiency attenuates inflammation in murine IBD models. Mucosal Immunol. 2019;12:200–11. https://doi.org/10.1038/s41385-018-0091-7.
67. Galleggiante V, De Santis S, Liso M, et al. Quercetin-induced miR-369-3p suppresses chronic inflammatory response targeting C/EBP-β. Mol Nutr Food Res. 2019;63:e1801390. https://doi.org/10.1002/mnfr.201801390.
68. Arao Y, Nakayama M, Tsuji Y, et al. EpisomiR, a new family of miRNAs, and its possible roles in human diseases. Biomedicines. 2022;10:1280. https://doi.org/10.3390/biomedicines10061280.
69. Mohammadi A, Kelly OB, Filice M, et al. Differential expression of microRNAs in peripheral blood mononuclear cells identifies autophagy and TGF-beta-related signatures aberrantly expressed in inflammatory bowel disease. J Crohns Colitis. 2018;12:568–81. https://doi.org/10.1093/ecco-jcc/jjy010.
70. Xiao X, Mao X, Chen D, et al. MiRNAs can affect intestinal epithelial barrier in inflammatory bowel disease. Front Immunol. 2022;13:868229. https://doi.org/10.3389/fimmu.2022.868229.
71. Tian Y, Xu J, Li Y, et al. MicroRNA-31 reduces inflammatory signaling and promotes regeneration in colon epithelium, and delivery of mimics in microspheres reduces colitis in mice. Gastroenterology. 2019;156:2281-96.e6. https://doi.org/10.1053/j.gastro.2019.02.023.
72. Casado-Bedmar M, Viennois E. MicroRNA and gut microbiota: tiny but mighty-novel insights into their cross-talk in inflammatory bowel disease pathogenesis and therapeutics. J Crohns Colitis. 2022;16:992–1005. https://doi.org/10.1093/ecco-jcc/jjab223.
73. Stiegeler S, Mercurio K, Iancu MA, et al. The Impact of microRNAs during inflammatory bowel disease: effects on the mucus layer and intercellular junctions for gut permeability. Cells. 2021;10:3358. https://doi.org/10.3390/cells10123358.
74. Nakata K, Sugi Y, Narabayashi H, et al. Commensal microbiota-induced microRNA modulates intestinal epithelial permeability through the small GTPase ARF4. J Biol Chem. 2017;292:15426–33. https://doi.org/10.1074/jbc.M117.788596.
75. Wang M, Guo J, Zhao YQ, et al. IL-21 mediates microRNA-423–5p/claudin-5 signal pathway and intestinal barrier function in inflammatory bowel disease. Aging (Albany NY). 2020;12:16099–110. https://doi.org/10.18632/aging.103566.
76. Muenchau S, Deutsch R, De Castro IJ, et al. Hypoxic environment promotes barrier formation in human intestinal epithelial cells through regulation of microRNA 320a expression. Mol Cell Biol. 2019;39:e00553-e618. https://doi.org/10.1128/mcb.00553-18.
77. Chen T, Xue H, Lin R, et al. MiR-126 impairs the intestinal barrier function via inhibiting S1PR2 mediated activation of PI3K/AKT signaling pathway. Biochem Biophys Res Commun. 2017;494:427–32. https://doi.org/10.1016/j.bbrc.2017.03.043.
78. Levine B, Kroemer G. Biological functions of autophagy genes: a disease perspective. Cell. 2019;176:11–42. https://doi.org/10.1016/j.cell.2018.09.048.
79. Zhai Z, Wu F, Dong F, et al. Human autophagy gene ATG16L1 is post-transcriptionally regulated by miR142-3p. Autophagy. 2014;10:468–79. https://doi.org/10.4161/auto.27553.
80. Brooks-Warburton J, Modos D, Sudhakar P, et al. A systems genomics approach to uncover patient-specific pathogenic pathways and proteins in ulcerative colitis. Nat Commun. 2022;13:2299. https://doi.org/10.1038/s41467-022-29998-8.
81. Wang S, Huang Y, Zhou C, et al. The role of autophagy and related micrornas in inflammatory bowel disease. Gastroenterol Res Pract. 2018;2018:7565076. https://doi.org/10.1155/2018/7565076.
82. Kim H, Banerjee N, Barnes RC, et al. Mango polyphenolics reduce inflammation in intestinal colitis-involvement of the miR-126/PI3K/AKT/mTOR axis in vitro and in vivo. Mol Carcinog. 2017;56:197–207. https://doi.org/10.1002/mc.22484.
83. Pegtel DM, Gould SJ. Exosomes. Annu Rev Biochem. 2019;88:487–514. https://doi.org/10.1146/annurev-biochem-013118-111902.
84. Mirzaei R, Zamani F, Hajibaba M, et al. The pathogenic, therapeutic and diagnostic role of exosomal microRNA in the autoimmune diseases. J Neuroimmunol. 2021;358:577640. https://doi.org/10.1016/j.jneuroim.2021.577640.
85. Cao Y, Wang Z, Yan Y, et al. Enterotoxigenic *Bacteroides-fragilis* promotes intestinal inflammation and malignancy by inhibiting exosome-packaged miR-149-3p. Gastroenterology. 2021;161:1552-66.e12. https://doi.org/10.1053/j.gastro.2021.08.003.
86. Kang J, Zhang Z, Wang J, et al. HucMSCs attenuate IBD through releasing miR148b-5p to inhibit the expression of 15-lox-1 in macrophages. Mediators Inflamm. 2019;2019:6953963. https://doi.org/10.1155/2019/6953963.
87. Larabi A, Dalmasso G, Delmas J, et al. Exosomes transfer miRNAs from cell-to-cell to inhibit autophagy during infection with Crohn's disease-associated adherent-invasive *E. coli*. Gut Microbes. 2020;11:1677–94. https://doi.org/10.1080/19490976.2020.1771985.
88. 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.
89. 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.
90. 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.
91. Scalavino V, Piccinno E, Bianco G, et al. The increase of miR-195-5p reduces intestinal permeability in ulcerative colitis, modulating tight junctions' expression. Int J Mol Sci. 2022;23:5840. https://doi.org/10.3390/ijms23105840.
92. He C, Yu T, Shi Y, et al. MicroRNA 301A Promotes intestinal inflammation and colitis-associated cancer development by inhibiting BTG1. Gastroenterology. 2017;152:1434-48.e15. https://doi.org/10.1053/j.gastro.2017.01.049.

93. Rawat M, Nighot M, Al-Sadi R, et al. IL1b increases intestinal tight junction permeability by up-regulation of miR200C-3p, which degrades occludin mRNA. Gastroenterology. 2020;159:1375–89. https://doi.org/10.1053/j.gastro.2020.06.038.
94. Li J, Zhang J, Guo H, et al. Critical role of alternative M2 skewing in miR-155 deletion-mediated protection of colitis. Front Immunol. 2018;9:904. https://doi.org/10.3389/fimmu.2018.00904.
95. Ma YS, Wu TM, Ling CC, et al. M2 macrophage-derived exosomal microRNA-155-5p promotes the immune escape of colon cancer by downregulating ZC3H12B. Mol Ther Oncolytics. 2021;20:484–98. https://doi.org/10.1016/j.omto.2021.02.005.
96. Liu H, Liang J, Zhong Y, et al. Dendrobium officinale polysaccharide alleviates intestinal inflammation by promoting small extracellular vesicle packaging of miR-433-3p. J Agric Food Chem. 2021;69:13510–23. https://doi.org/10.1021/acs.jafc.1c05134.
97. Song L, Chang R, Sun X, et al. Macrophage-derived EDA-A2 inhibits intestinal stem cells by targeting miR-494/EDA2R/β-catenin signaling in mice. Commun Biol. 2021;4:213. https://doi.org/10.1038/s42003-021-01730-0.
98. Cai X, Zhang ZY, Yuan JT, et al. HucMSC-derived exosomes attenuate colitis by regulating macrophage pyroptosis via the miR-378a-5p/NLRP3 axis. Stem Cell Res Ther. 2021;12:416. https://doi.org/10.1186/s13287-021-02492-6.
99. Jie F, Xiao S, Qiao Y, et al. Kuijieling decoction suppresses NLRP3-Mediated pyroptosis to alleviate inflammation and experimental colitis in vivo and in vitro. J Ethnopharmacol. 2021;264:113243. https://doi.org/10.1016/j.jep.2020.113243.
100. Zhu X, Zhu Y, Li C, et al. 1,25-Dihydroxyvitamin D regulates macrophage polarization and ameliorates experimental inflammatory bowel disease by suppressing miR-125b. Int Immunopharmacol. 2019;67:106–18. https://doi.org/10.1016/j.intimp.2018.12.015.
101. Zhu Y, Gu L, Li Y, et al. MiR-148a inhibits colitis and colitis-associated tumorigenesis in mice. Cell Death Differ. 2017;24:2199–209. https://doi.org/10.1038/cdd.2017.151.
102. Shamran H, Singh NP, Zumbrun EE, et al. Fatty acid amide hydrolase (FAAH) blockade ameliorates experimental colitis by altering microRNA expression and suppressing inflammation. Brain Behav Immun. 2017;59:10–20. https://doi.org/10.1016/j.bbi.2016.06.008.
103. 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/ β-catenin signalling axis. J Crohns Colitis. 2021;15:665–77. https://doi.org/10.1093/ecco-jcc/jjaa214.
104. Ghorpade DS, Sinha AY, Holla S, et al. NOD2-nitric oxide-responsive microRNA-146a activates Sonic hedgehog signaling to orchestrate inflammatory responses in murine model of inflammatory bowel disease. J Biol Chem. 2013;288:33037–48. https://doi.org/10.1074/jbc.M113.492496.
105. Yang J, Pei G, Sun X, et al. RhoB affects colitis through modulating cell signaling and intestinal microbiome. Microbiome. 2022;10:149. https://doi.org/10.1186/s40168-022-01347-3.
106. Zhang M, Yang D, Yu H, et al. MicroRNA-497 inhibits inflammation in DSS-induced IBD model mice and lipopolysaccharide-induced RAW264.7 cells via Wnt/β-catenin pathway. Int Immunopharmacol. 2021;101:108318. https://doi.org/10.1016/j.intimp.2021.108318.
107. Wu CX, Cheng J, Wang YY, et al. MicroRNA expression profiling of macrophage line Raw264.7 infected by *Candida albicans*. Shock. 2017;47:520–30. https://doi.org/10.1097/shk.0000000000000766.
108. Zhang M, Xia Z, Yang X, et al. Specific microRNA/mRNA expression profiles and novel immune regulation mechanisms are induced in THP-1 macrophages by in vitro exposure to Trichosporon asahii. Mycoses. 2021;64:831–40. https://doi.org/10.1111/myc.13268.
109. Perez-Sanchez C, Barbera Betancourt A, Lyons PA, et al. MiR-374a-5p regulates inflammatory genes and monocyte function in patients with inflammatory bowel disease. J Exp Med. 2022;219:e20211366. https://doi.org/10.1084/jem.20211366.
110. Marschner D, Falk M, Javorniczky NR, et al. MicroRNA-146a regulates immune-related adverse events caused by immune checkpoint inhibitors. JCI Insight. 2020;5:e132334. https://doi.org/10.1172/jci.insight.132334.
111. Bui TM, Sumagin R. Progressing from recurring tissue injury to genomic instability: a new mechanism of neutrophil pathogenesis. DNA Cell Biol. 2019;38:747–53. https://doi.org/10.1089/dna.2019.4842.
112. Butin-Israeli V, Bui TM, Wiesolek HL, et al. Neutrophil-induced genomic instability impedes resolution of inflammation and wound healing. J Clin Invest. 2019;129:712–26. https://doi.org/10.1172/jci122085.
113. Neudecker V, Haneklaus M, Jensen O, et al. Myeloid-derived miR-223 regulates intestinal inflammation via repression of the NLRP3 inflammasome. J Exp Med. 2017;214:1737–52. https://doi.org/10.1084/jem.20160462.
114. Jiang H, Wang P, Li X, et al. Restoration of miR17/20a in solid tumor cells enhances the natural killer cell antitumor activity by targeting Mekk2. Cancer Immunol Res. 2014;2:789–99. https://doi.org/10.1158/2326-6066.Cir-13-0162.
115. Altamemi I, Murphy EA, Catroppo JF, et al. Role of microRNAs in resveratrol-mediated mitigation of colitis-associated tumorigenesis in Apc(Min/$^{+}$) mice. J Pharmacol Exp Ther. 2014;350:99–109. https://doi.org/10.1124/jpet.114.213306.
116. Wu W, He C, Liu C, et al. MiR-10a inhibits dendritic cell activation and Th1/Th17 cell immune responses in IBD. Gut. 2015;64:1755–64. https://doi.org/10.1136/gutjnl-2014-307980.
117. Fukata T, Mizushima T, Nishimura J, et al. The supercarbonate apatite-microRNA complex inhibits dextran sodium sulfate-induced colitis. Mol Ther Nucleic Acids. 2018;12:658–71. https://doi.org/10.1016/j.omtn.2018.07.007.
118. Krishnachaitanya SS, Liu M, Fujise K, et al. MicroRNAs in inflammatory bowel disease and its complications. Int J Mol Sci. 2022;23:8751. https://doi.org/10.3390/ijms23158751.
119. Lim CX, Lee B, Geiger O, et al. MiR-181a modulation of ERK-MAPK signaling sustains DC-sign expression and limits activation of monocyte-derived dendritic cells. Cell Rep. 2020;30:3793-3805.e5. https://doi.org/10.1016/j.celrep.2020.02.077.
120. Vieujean S, Caron B, Haghnejad V, et al. Impact of the exposome on the epigenome in inflammatory bowel disease patients and animal models. Int J Mol Sci. 2022;23:7611. https://doi.org/10.3390/ijms23147611.
121. Zhou H, Xiao J, Wu N, et al. MicroRNA-223 Regulates the differentiation and function of intestinal dendritic cells and macrophages by targeting C/EBPβ. Cell Rep. 2015;13:1149–60. https://doi.org/10.1016/j.celrep.2015.09.073.
122. Lin Z, Xie X, Gu M, et al. MicroRNA-144/451 decreases dendritic cell bioactivity via targeting interferon-regulatory factor 5 to limit DSS-induced colitis. Front Immunol. 2022;13:928593. https://doi.org/10.3389/fimmu.2022.928593.
123. Shi Y, Dai S, Qiu C, et al. MicroRNA-219a-5p suppresses intestinal inflammation through inhibiting Th1/Th17-mediated immune responses in inflammatory bowel disease. Mucosal Immunol. 2020;13:303–12. https://doi.org/10.1038/s41385-019-0216-7.

124. Huang J, Xu X, Yang J. MiRNAs alter T helper 17 cell fate in the pathogenesis of autoimmune diseases. Front Immunol. 2021;12:593473. https://doi.org/10.3389/fimmu.2021.593473.
125. Amerikanou C, Papada E, Gioxari A, et al. Mastiha has efficacy in immune-mediated inflammatory diseases through a microRNA-155 Th17 dependent action. Pharmacol Res. 2021;171:105753. https://doi.org/10.1016/j.phrs.2021.105753.
126. Singh UP, Murphy AE, Enos RT, et al. MiR-155 deficiency protects mice from experimental colitis by reducing T helper type 1/type 17 responses. Immunology. 2014;143:478–89. https://doi.org/10.1111/imm.12328.
127. Shi T, Xie Y, Fu Y, et al. The signaling axis of microRNA-31/interleukin-25 regulates Th1/Th17-mediated inflammation response in colitis. Mucosal Immunol. 2017;10:983–95. https://doi.org/10.1038/mi.2016.102.
128. Yang R, Huang H, Cui S, et al. IFN-γ promoted exosomes from mesenchymal stem cells to attenuate colitis via miR-125a and miR-125b. Cell Death Dis. 2020;11:603. https://doi.org/10.1038/s41419-020-02788-0.
129. Chinen I, Nakahama T, Kimura A, et al. The aryl hydrocarbon receptor/microRNA-212/132 axis in T cells regulates IL-10 production to maintain intestinal homeostasis. Int Immunol. 2015;27:405–15. https://doi.org/10.1093/intimm/dxv015.
130. Chao G, Li X, Ji Y, et al. MiR-155 controls follicular Treg cell-mediated humoral autoimmune intestinal injury by inhibiting CTLA-4 expression. Int Immunopharmacol. 2019;71:267–76. https://doi.org/10.1016/j.intimp.2019.03.009.
131. Ge Y, Sun M, Wu W, et al. MicroRNA-125a suppresses intestinal mucosal inflammation through targeting ETS-1 in patients with inflammatory bowel diseases. J Autoimmun. 2019;101:109–20. https://doi.org/10.1016/j.jaut.2019.04.014.
132. Xue X, Cao AT, Cao X, et al. Downregulation of microRNA-107 in intestinal CD11c(+) myeloid cells in response to microbiota and proinflammatory cytokines increases IL-23p19 expression. Eur J Immunol. 2014;44:673–82. https://doi.org/10.1002/eji.201343717.
133. Proença MA, Biselli JM, Succi M, et al. Relationship between *Fusobacterium nucleatum*, inflammatory mediators and microRNAs in colorectal carcinogenesis. World J Gastroenterol. 2018;24:5351–65. https://doi.org/10.3748/wjg.v24.i47.5351.
134. Vollmers S, Lobermeyer A, Körner C. The new kid on the block: HLA-C, a key regulator of natural killer cells in viral immunity. Cells. 2021;10:3108. https://doi.org/10.3390/cells10113108.
135. Yang Y, Liu L, Liu X, et al. Extracellular vesicles derived from *Trichinella spiralis* muscle larvae ameliorate TNBS-induced colitis in mice. Front Immunol. 2020;11:1174. https://doi.org/10.3389/fimmu.2020.01174.
136. Zhang T, Yu J, Zhang Y, et al. *Salmonella enterica* serovar enteritidis modulates intestinal epithelial miR-128 levels to decrease macrophage recruitment via macrophage colony-stimulating factor. J Infect Dis. 2014;209:2000–11. https://doi.org/10.1093/infdis/jiu006.
137. Soroosh A, Koutsioumpa M, Pothoulakis C, et al. Functional role and therapeutic targeting of microRNAs in inflammatory bowel disease. Am J Physiol Gastrointest Liver Physiol. 2018;314:G256–62. https://doi.org/10.1152/ajpgi.00268.2017.
138. Gong L, Xiao J, Yi J, et al. Immunomodulatory effect of serum exosomes from Crohn disease on macrophages via Let-7b-5p/TLR4 signaling. Inflamm Bowel Dis. 2022;28:96–108. https://doi.org/10.1093/ibd/izab132.
139. Luan X, Sansanaphongpricha K, Myers I, et al. Engineering exosomes as refined biological nanoplatforms for drug delivery. Acta Pharmacol Sin. 2017;38:754–63. https://doi.org/10.1038/aps.2017.12.
140. Zhang M, Merlin D. Nanoparticle-based oral drug delivery systems targeting the colon for treatment of ulcerative colitis. Inflamm Bowel Dis. 2018;24:1401–15. https://doi.org/10.1093/ibd/izy123.
141. Nitzan O, Elias M, Peretz A, et al. Role of antibiotics for treatment of inflammatory bowel disease. World J Gastroenterol. 2016;22:1078–87. https://doi.org/10.3748/wjg.v22.i3.1078.
142. Carmona EM, Limper AH. Overview of treatment approaches for fungal infections. Clin Chest Med. 2017;38:393–402. https://doi.org/10.1016/j.ccm.2017.04.003.
143. Panpetch W, Hiengrach P, Nilgate S, et al. Additional *Candida albicans* administration enhances the severity of dextran sulfate solution induced colitis mouse model through leaky gut-enhanced systemic inflammation and gut-dysbiosis but attenuated by *Lactobacillus rhamnosus* L34. Gut Microbes. 2020;11:465–80. https://doi.org/10.1080/19490976.2019.1662712.
144. Kelly CR, Kahn S, Kashyap P, et al. Update on fecal microbiota transplantation 2015: indications, methodologies, mechanisms, and outlook. Gastroenterology. 2015;149:223–37. https://doi.org/10.1053/j.gastro.2015.05.008.
145. Eindor-Abarbanel A, Healey GR, Jacobson K. Therapeutic advances in gut microbiome modulation in patients with inflammatory bowel disease from pediatrics to adulthood. Int J Mol Sci. 2021;22:12506. https://doi.org/10.3390/ijms222212506.
146. Koelink PJ, Bloemendaal FM, Li B, et al. Anti-TNF therapy in IBD exerts its therapeutic effect through macrophage IL-10 signalling. Gut. 2020;69:1053–63. https://doi.org/10.1136/gutjnl-2019-318264.
147. Bortlik M, Duricova D, Malickova K, et al. Infliximab trough levels may predict sustained response to infliximab in patients with Crohn's disease. J Crohns Colitis. 2013;7:736–43. https://doi.org/10.1016/j.crohns.2012.10.019.
148. Sandborn WJ, Feagan BG, Marano C, et al. Subcutaneous golimumab induces clinical response and remission in patients with moderate-to-severe ulcerative colitis. Gastroenterology. 2014;146:85–95. https://doi.org/10.1053/j.gastro.2013.05.048.
149. Ferretti F, Cannatelli R, Monico MC, et al. An update on current pharmacotherapeutic options for the treatment of ulcerative colitis. J Clin Med. 2022;11:2302. https://doi.org/10.3390/jcm11092302.
150. Elbadry M, Medhat MA, Zaky S, et al. Ulcerative colitis as a possible sequela of COVID-19 Infection: the endless story. Arab J Gastroenterol. 2022;23:134–7. https://doi.org/10.1016/j.ajg.2022.01.006.
151. Neurath MF. COVID-19 and immunomodulation in IBD. Gut. 2020;69:1335–42. https://doi.org/10.1136/gutjnl-2020-321269.
152. Lv L, Gu S, Jiang H, et al. Gut mycobiota alterations in patients with COVID-19 and H1N1 infections and their associations with clinical features. Commun Biol. 2021;4:480. https://doi.org/10.1038/s42003-021-02036-x.
153. Zuo T, Zhan H, Zhang F, et al. Alterations in fecal fungal microbiome of patients with COVID-19 during time of hospitalization until discharge. Gastroenterology. 2020;159:1302-10.e5. https://doi.org/10.1053/j.gastro.2020.06.048.
154. Gracie DJ, Hamlin PJ, Ford AC. The influence of the brain-gut axis in inflammatory bowel disease and possible implications for treatment. Lancet Gastroenterol Hepatol. 2019;4:632–42. https://doi.org/10.1016/s2468-1253(19)30089-5.
155. Karaivazoglou K, Konstantakis C, Tourkochristou E, et al. Non-alcoholic fatty liver disease in inflammatory bowel disease patients. Eur J Gastroenterol Hepatol. 2020;32:903–6. https://doi.org/10.1097/meg.0000000000001679.
156. Sencio V, Machado MG, Trottein F. The lung-gut axis during viral respiratory infections: the impact of gut dysbiosis on secondary disease outcomes. Mucosal Immunol. 2021;14:296–304. https://doi.org/10.1038/s41385-020-00361-8.

157. Li Y, Liu Y, Shi Z. Advances in the understanding and treatment of inflammatory bowel disease in Chinese medicine. J Clin Intern Med. 2021;38:87–9.