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REVIEW

MicroRNA signatures in the pathogenesis and therapy of inflammatory bowel disease

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Abstract

Inflammatory bowel disease (IBD) is a persistent inflammatory illness of the gastrointestinal tract (GIT) triggered by an inappropriate immune response to environmental stimuli in genetically predisposed persons. Unfortunately, IBD patients' quality of life is negatively impacted by the symptoms associated with the disease. The exact etiology of IBD pathogenesis is not fully understood, but the emerging research indicated that the microRNA (miRNA) plays an important role. miRNAs have been documented to possess a significant role in regulating pro- and anti-inflammatory pathways, in addition to their roles in several physiological processes, including cell growth, proliferation, and apoptosis. Variations in the miRNA profiles might be a helpful prognostic indicator and a valuable tool in the differential diagnosis of IBD. Most interestingly, these miRNAs have a promising therapeutic target in several pre-clinical animal studies and phase 2 clinical studies to alleviate inflammation and improve patient's quality of life. This comprehensive review discusses the current knowledge about the significant physiological role of different miRNAs in the health of the intestinal immune system and addresses the role of the most relevant differentially expressed miRNAs in IBD, identify their potential targets, and emphasize their diagnostic and therapeutic potential for future research.

Keywords MicroRNA (miRNA) · Inflammatory bowel disease (IBD) · miRNA signature · Pathogenesis · Therapy

Introduction

Inflammatory bowel disease (IBD) is a chronic inflammatory and autoimmune disorder affecting the gastrointestinal tract (GIT) and is characterized by increased intestinal permeability as well as imbalanced and hyperactive immunological responses caused by environmental factors such as dietary components and gut microbiome. IBD is classified into two subtypes: ulcerative colitis (UC) and Crohn's disease (CD), each of which has unique clinical and pathological features [1]. UC is characterized by continuous and superficial inflammation of the colon or rectum mucosa that may result in erosion and ulcers (Fig. 1). On the other side, CD affects any part of the GIT, from the mouth to the anus, and is characterized by discontinuous transmural inflammation that affects all layers of the intestinal wall (Fig. 1) [2], and may be complicated with time into abscesses, strictures, or fistulas [3, 4]. CD and UC mostly affect adolescents, resulting in abdominal pain, malabsorption, bloody diarrhea, weight loss, fatigue, and decreased quality of life. Prolonged and uncontrolled inflammation also raises the chance of colorectal cancer (CRC) and increases the mortality rate to 10–15% [5].

Since the exact pathogenesis of IBD is unclear, it is speculated that it may be triggered by an interaction between immune, genetic, and environmental factors, including gut microbiome (Fig. 2) [2]. Around 240 genetic susceptibility

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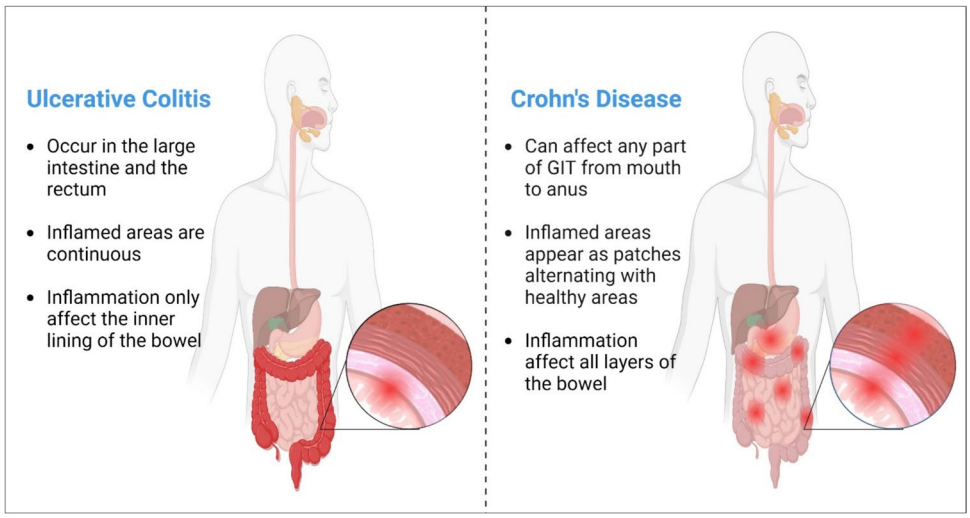

Fig. 1 Difference between two forms of IBD. Ulcerative colitis (left side); which occurs only in the colon and rectum and is characterized by the continuous appearance of inflammation and an inner layer of the bowel is involved in inflammation. **Crohn's disease (right side)**; which occurs in any part of GIT and characterized with the patchy appearance of inflammation and all layers of bowel involved in inflammation. **Created with BioRender.com**

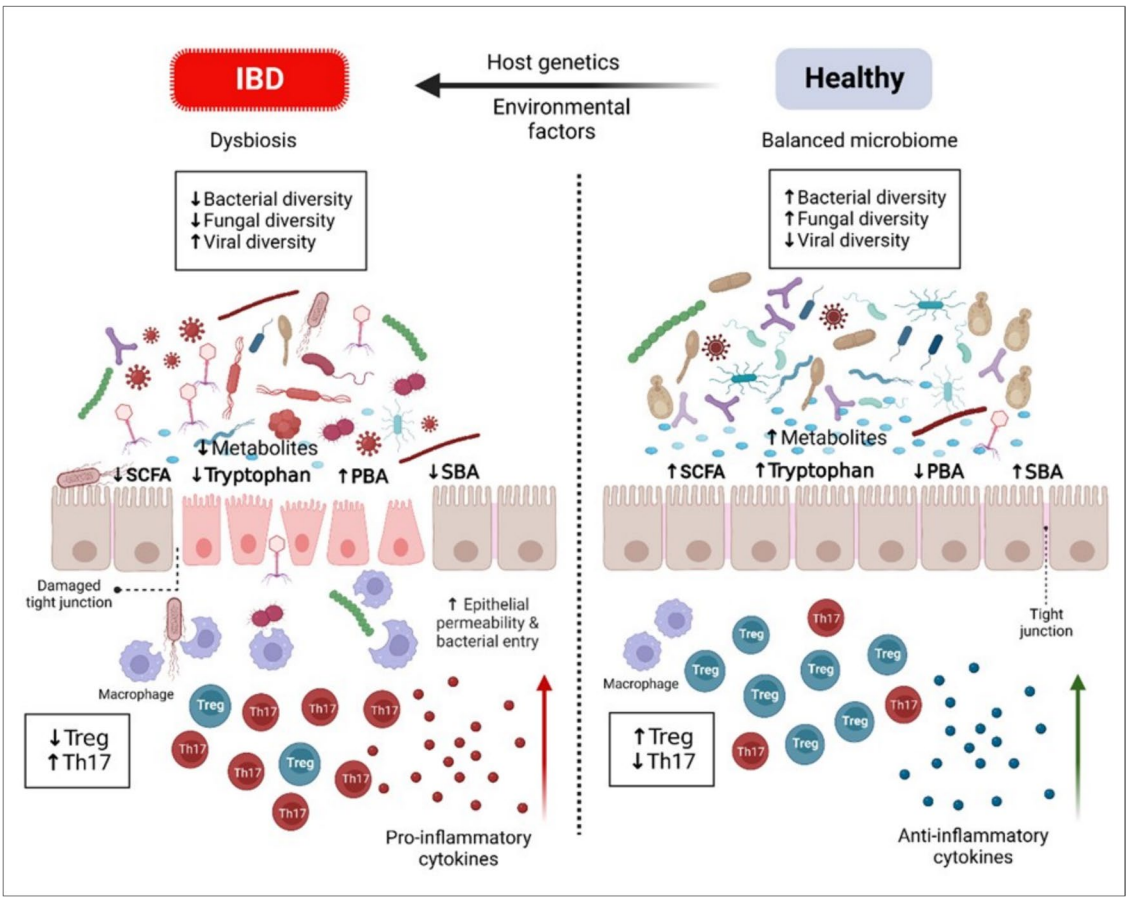

Fig. 2 Hypothesized pathogenesis of IBD. It is speculated that IBD is a multifactorial disease and may be triggered by a complex interaction between immune, genetic, and environmental factors, including gut microbiome. In a healthy state, diversity, and eubiosis of the gut microbiome largely participate in the health of the intestinal barrier and tight junction, mainly through their metabolites. This keeps the balance between immune cells with the upregulation of anti-inflammatory Treg cells. In the IBD case, dysbiosis of gut microbiome is persistent and leads to damage to intestinal barrier and tight junctions with a subsequent increase of intestinal permeability for pathogens and triggering of immune cells and inflammatory reactions. **Created with BioRender.com**

loci for IBD have been discovered by genome-wide association studies (GWASs) [6–9]. Growing molecular studies revealed that microRNA (miRNA) plays a significant role in the pathogenesis of IBD [10].

miRNAs are short (~22 nucleotides), non-coding, single-strand RNA molecules that regulate gene expression to affect several biological processes [11]. They work by binding to the 3' untranslated region (UTR) of a target mRNA, preventing translation and limiting its expression [12]. Recent research findings indicate that miRNAs may have a positive or negative impact on the incidence and progression of IBD [13–16]. Additionally, miRNAs serve as therapeutic targets and biomarkers for diagnosis. miRNAs may help distinguish between UC and CD, in addition to being used as biomarkers of response to therapy, and disease activity, and possibly be used as predictive indicators of disease severity and the development of complications such as stenosis, penetrating disease, as well as CRC [17, 18]. In this regard, this review aims to give detailed insights about miRNA signatures in pathogenesis and differential diagnosis of IBD.

miRNA: general overview

miRNA is a kind of short noncoding RNA that is about 18–22 nucleotides long [19, 20]. miRNAs were initially discovered in 1993 while studying *Lin*-4 gene in the nematode model, *Caenorhabditis elegans*, to find abnormalities in postembryonic maturation [21]. The ability of lin-4, the first miRNA to be identified, to downregulate the nuclear protein *lin-14* was discovered to be responsible for starting the second stage of larval development [21, 22]. In 2000, Let-7, a second miRNA discovered in *C. elegans*, seemed to be extensively conserved throughout creatures including humans [23, 24]. Based on historical data, miRNAs can significantly suppress the expression of certain genes [25, 26]. Within a particular cell type, a miRNA can target numerous mRNAs, and one mRNA is frequently the target of many miRNAs since complete complementarity is not necessary for miRNAs to recognize their targets [27]. Therefore, almost 30% of protein-coding genomes are regulated partially by miRNAs [28].

miRNAs affect several physiological processes, such as cell cycle regulation and homeostasis, cell survival, differentiation, expansion, and apoptosis. In addition, some miRNAs influence the differentiation of cells in the gut epithelium [25, 26]. As a result, miRNAs possess a significant role in the control of a variety of immune-mediated diseases, including IBD [27, 29–33].

miRNA genes are found within the host genome. miRNA transcription is first started in the nucleus where miRNA is transcribed into primary transcript (pri-miRNA) by RNA polymerase [34, 35]. Then, a protein complex made up of the RNAse-III, Drosha, and DiGeorge critical region 8 (DGCR8) cleaves pri-miRNA, producing precursor miRNA (pre-miRNA), a chain of 60–70 nucleotides [36–38]. After these, pre-miRNA is transported to the cytoplasm via the Exportin-5 (Exp5)—RanGTP complex [39]. Pre-miRNA is finally cleaved into its mature state by the RNase III enzyme, dicer, which is then permanently integrated into an RNA-induced silencing complex (RISC). The RISC binds to complementary sequences in the 3′-UTR of target mRNA molecules under the guidance of the miRNA, which either causes translational suppression or mRNA destruction (Fig. 3) [11, 40]. Throughout the miRNA biogenesis process, several variables may impact the stage of maturation of miRNA. These include controlling transcription, editing, controlling the turnover of miRNA, and cleaving stem-loop structures via the enzymes Drosha and Dicer. All of these processes contribute to a signaling network that adjusts gene expression as a consequence of environmental or cellular alterations [18].

Remarkably, miRNAs are found in a variety of bodily fluids, including cerebrospinal fluid, milk, saliva, feces, and urine, in addition to circulating in the human bloodstream in a stable form [41–44]. Since miRNAs play a role in the induction and progression of several illnesses, and since certain miRNAs are pathology-specific [45], research has been conducted on how variations in miRNA expression patterns may be used for prognostication, medication response prediction, and early diagnosis.

The significance of miRNAs in intestinal immune system regulation

Innate immune system

The innate immune system serves as the initial barrier of defense, responding quickly and non-specifically to immunological stimuli. Furthermore, the innate immune system communicates with and regulates the acquired immune system. Prior research has demonstrated the functions of miRNAs in controlling the innate immune system of the gut.

miR-29 was demonstrated to possess a significant impact in regulating dendritic cell activity in the gut [46]. Brain et al. [46] showed that miR-29 downregulates interleukin (IL)-23 through binding IL-12p40 mRNA directly and IL-23p19 mRNA indirectly in dendritic cells, resident in the gut, in response to intracellular microbe detector, nucleotide-binding oligomerization domain containing 2 (*NOD2*). Consequently, it was proposed that miR-29 might inhibit intestinal dendritic cells' proinflammatory function. Additionally, the authors demonstrated that animal models lacking miR-29 and having high levels of IL-23 in their intestines had worsened experimental colitis.

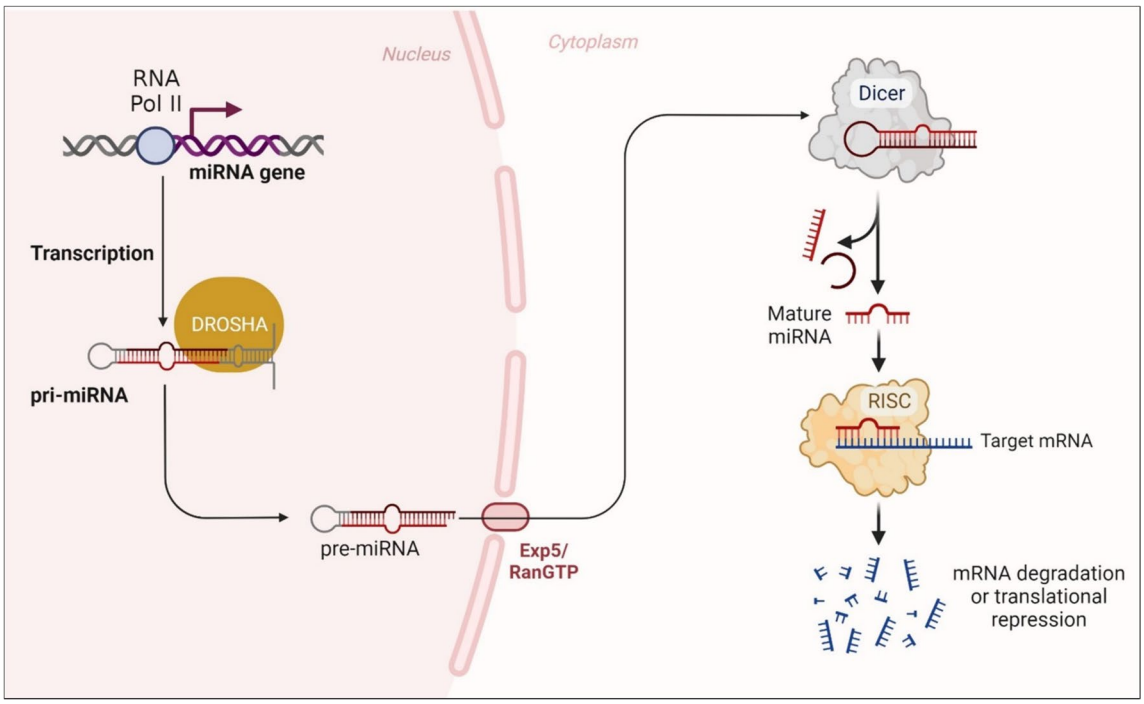

Fig. 3 A schematic representation of microRNA biosynthesis. miRNA transcription is first started in the nucleus where miRNA is transcribed into primary transcript (pri-miRNA) by RNA polymerase. Then, a protein complex made up of the RNAse-III, Drosha, and DiGeorge critical region 8 (DGCR8) cleaves pri-miRNA, producing precursor miRNA (pre-miRNA), a chain of 60–70 nucleotides. After these, pre-miRNA is transported to the cytoplasm via the Exportin-5 (Exp5)—RanGTP complex. Pre-miRNA is finally cleaved into its mature state by the RNase III enzyme, dicer, which is then permanently integrated into an RNA-induced silencing complex (RISC). The RISC binds to complementary sequences in the 3′- UTR of target mRNA molecules under the guidance of the miRNA, which either causes translational suppression or mRNA destruction. **Created with BioRender.com**

miR-223 was suggested to regulate the intestinal dendritic cells and macrophages. In this regard, Zhou et al. [266] found that intestinal dendritic cells and macrophages in miR-223-lacking mice exhibited a strong proinflammatory behavior. In the same study, the authors discovered that miR-223 targets the mRNA for CCAAT/enhancer binding protein β (C/EBPβ). Therefore, it was concluded that miR-223 directly targets C/EBPβ mRNA to inhibit the proinflammatory characteristics in intestinal dendritic cells and macrophages. According to Neudecker et al., mice lacking miR-223 exhibited exacerbated experimental colitis along with stimulation of the nucleotide-binding domain leucine-rich-containing family pyrin domain-containing-3 (NLRP3) inflammasome. Furthermore, colitis aggravation and NLRP3 stimulation were seen in animals lacking the miR-223 binding region in the NLRP3 3′ UTR. Amazingly, the colitis was reduced by the injection of miR-223 mimic.

miR-146b is thought to control the polarization of macrophages in the gut [47, 48]. According to a recent study [49], miR-146b was demonstrated to be downregulated in IBD mice and LPS-induced macrophages. Subsequent analysis revealed that miR-146b exerts its inhibitory effect through interaction with its target gene, Fibrinogen Like 2 (*FGL2*), as well as that FGL2 mediated the triggering of p38-MAPK, NLRP3, and NF-κB-p65. Consequently, it was confirmed that miR-146b could reduce M1 macrophage polarization and improve inflammatory behavior by blocking FGL2 in vitro. Furthermore, miR-146b overexpression reduced intestinal damage in vivo in IBD mice [49]. Peng et al. [50] demonstrated that IL-10 and LPS stimulated the production of miR-146b in macrophages and that IL-10-deficient macrophages showed decreased miR-146b expression. They also demonstrated that the miR-146b and mRNAs of interferon regulatory factor 5 (IRF5) may coexist on the same RISC, and miR-146b transfection mimic reduced LPS-induced IRF5 protein production and M1 macrophage activation, indicating that miR-146b targets IRF5 mRNA. Moreover, animals lacking miR-146b showed improved polarization of M1 macrophages. Based on these results, the authors hypothesized that the control of M1 macrophage activation in the gut is mostly dependent on the IL-10-miR-146b-IRF5 axis.

Reportedly, the activity of innate immune cells, such as neutrophils, natural killer cells, and innate lymphoid cells, is regulated by other miRNAs, including miR-20a, miR-34a, miR-24, miR-183, miR-150, and miR-155 [51]. More

research is needed to determine if these miRNAs possess significance in the innate immune system of the gut.

Acquired immune system

T-cell

miRNAs have a role in acquired immune cell (T- and B-cell) development as well. It has been demonstrated that the expression of miRNA was notably downregulated in effector T-cells that were actively dividing, while it was greatest in nonreplicating naïve T-cells and relatively inactive memory T-cells. According to recent investigations, the intestinal-acquired immune system is substantially regulated by miRNA-induced gene silencing.

Wang et al. [52] demonstrated that miR-34a suppresses Th17 cell development and proliferation in the large intestine by targeting the mRNAs of the IL-6 and IL-23 receptors, and it also inhibits Th17 migration to the epithelium by targeting the mRNA of chemokine (C–C motif) ligand 22 (CCL22). According to Takahashi et al. [53], miR-10a, which is particularly abundant in regulatory T (Treg) cells, is triggered by transforming growth factor-β (TGF-β) and retinoic acid. It targets nuclear receptor co-repressor 2 (Ncor2) mRNA and B-cell leukemia/lymphoma (Bcl) 6 mRNA in the Peyer's patches of the small intestine, attenuating the transformation of inducible Treg cells into follicular helper T (Th) cells. Additionally, they demonstrated that miR-10a inhibited Th-17 cell development, suggesting that miR-10a may have an anti-inflammatory role. In contrast, a recent study by Yang et al. [54] found that the CD4 + T cells miR-10a-deficient mice were less vulnerable to intestinal inflammation induced by dextran sulfate sodium (DSS). Additionally, they found that miR-10a reduced the production of IL-10 in the intestinal CD4 + T cells through targeting the *Prdm1* gene, which encodes transcription factor Blimp1. A study by Ge et al. [55] showed that IBD patients' colons have downregulated miR-125a, which is linked to suppression of proinflammatory cytokine secretion via targeting a transcription factor, E26 avian leukemia oncogene 1, 5′ domain (ETS-1), mRNA in CD4 + T cells. They also demonstrated that a lack of miR-125a aggravated the intestinal inflammation induced by trinitrobenzene sulphonic acid.

There is debate over the function of miR-155 in the T-cell response concerning intestinal inflammation. miR-155, which targets IL-2-inducible T-cell kinase mRNA, has been identified by Das et al. [56] to be implicated in TGF-β-induced inhibition of intestinal T-cell activation, including interferon-γ (IFN-γ) and IL-2 generation. In comparison, Chao et al. [57] found that the DDS mice model with overexpressed miR-155 in Treg cell displayed spontaneous autoimmunity and worsening of colitis. Additionally, to further inhibit the regulatory function of Treg cells, miR-155 specifically targeted the cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) mRNA in Treg cells.

Sanctuary et al. [58] noted that a reduced Treg function was seen in both humans and mice with elevated miR-106a levels. This was due to the inhibition of post-transcriptional control of IL-10 release through binding of NF-κB promoter. Thus, a lack of miR-106a resulted in increased production of IL-10 and induction of Treg cells, as well as a reduction in intestinal inflammation by blocking the proliferation of Th1 and Th17 cell subsets in the intestinal lamina propria.

Mikami et al. [59] discovered that miR-221 and miR-222 are essential components for the intestinal Th17 cell response which are activated upon IL-23 stimulation to limit the extent of the proinflammatory response. The authors reported that miR-221 and miR-222 targeted the mRNAs of the MAF bZIP transcription factor (Maf) and the IL-23 receptor to inhibit the proliferation of intestinal Th17 cells upon IL-23 stimulation. Any loss of expression of miR-221 and miR-222 increased the susceptibility of mucosal barrier damage in mice models. Consequently, it was proposed that miR-221 and miR-222 affect the proinflammatory Th17 cell response in the gut by acting as negative feedback regulators downstream of IL-23.

B-cell

Intestinal B cells also have a role in miRNA silencing, in addition to T cells. Most miRNAs expressed in B cells are unique to different developmental stages, so, variations in miRNA expression can be utilized to categorize B-cell subpopulations [60]. Zhou et al. [61] discovered that miR-150 controls the transformation of the pro- to the pre-B-cell stage, and that upregulation of this miRNA suppresses B-cell growth. Vigorito et al. [62] revealed that miR-155 is involved in the control of humoral immunity by boosting the generation of high-affinity IgG antibodies by B2 cells through binding to its target, Pu.1 transcription factor. Moreover, Casali et al. [63] showed that miR-146a binds to the mRNA of decapentaplegic (Smad)2, Smad3, and Smad4; this reduces class-switch recombination (CSR) to immunoglobulin A (IgA). They also demonstrated that there were more IgA + B cells in the gut of mice lacking miR-146a.

miRNAs and autophagy in IBD

The autophagy process is well known for maintaining cellular homeostasis [64] and for being crucial to host defense, particularly in controlling inflammation [65, 66]. Any abnormalities in this process can result in several issues, such as intracellular pathogen clearance, innate immune dysfunction, as well as intestinal epithelial dysfunction [67, 68]. Recent study has also shown that miRNAs play essential

roles in IBD and regulate autophagy via many cellular pathways. miRNAs can modulate intestinal barrier integrity and innate intestinal immunity through interaction with autophagy genes involved in IBD such as *ATG16L1*, *IRGM*, and *NOD2* (Fig. 4). These miRNAs play a role in autophagy by modulating the unfolded protein response (UPR) during endoplasmic reticulum stress, thus leading to intestinal fibrosis in IBD patients [69]. Research on cellular pathways has revealed that miRNAs can influence inflammatory mediators and pro- or anti-inflammatory effects by controlling NF-κB and mTOR signaling, which in turn can stimulate or inhibit intestinal autophagy [70, 71] (Fig. 4).

miRNAs and intestinal epithelial barrier in IBD

The intestinal epithelial barrier is a single layer of cells that prevents the body's immune cells from attacking millions of commensal microbes resident in the gut of healthy adults. It is a special structure, and the small and large intestines have very different cellular compositions that change over intestinal lengths [72]. The intestinal barrier (IB), which is made up of junctional complexes and intestinal epithelial cells (IECs), is a selectively permeable membrane that helps to sustain intestinal homeostasis. As a result, loss of IB function is linked to gastrointestinal disorders such as IBD [73]. Numerous unique IECs are found in the intestinal epithelium, including enterocytes (which aid in the absorption of nutrients), enteroendocrine cells (which secrete hormones), goblet cells (which produce mucus), Tuft cells (chemosensory cells) and Microfold (M) cells (which aid in the uptake of antigens) [74]. Additionally, the small intestine contains Paneth cells that produce proteins like epidermal growth factor (EGF) to preserve the stem cell niche and promote intestinal regeneration [75]. Moreover, Paneth cells release antimicrobial peptides such as defensins and produce genes including *IRGM1*, *NOD2*, and *ATG16L1*, which are dysregulated in CD patients. Likewise, goblet cell malfunction has been linked to problems in mucus synthesis and increased vulnerability to developing UC [72].

Several studies have reported that miRNA possesses a significant role in the proliferation, differentiation, and repair of IEC [76–82] as well as the formation and regulation of tight junctions (TJ) [83–89]. Thus, miRNA is considered one of the most important players in controlling IB integrity and permeability. To illustrate, the antibacterial capabilities of Paneth cells were boosted, and IEC proliferation

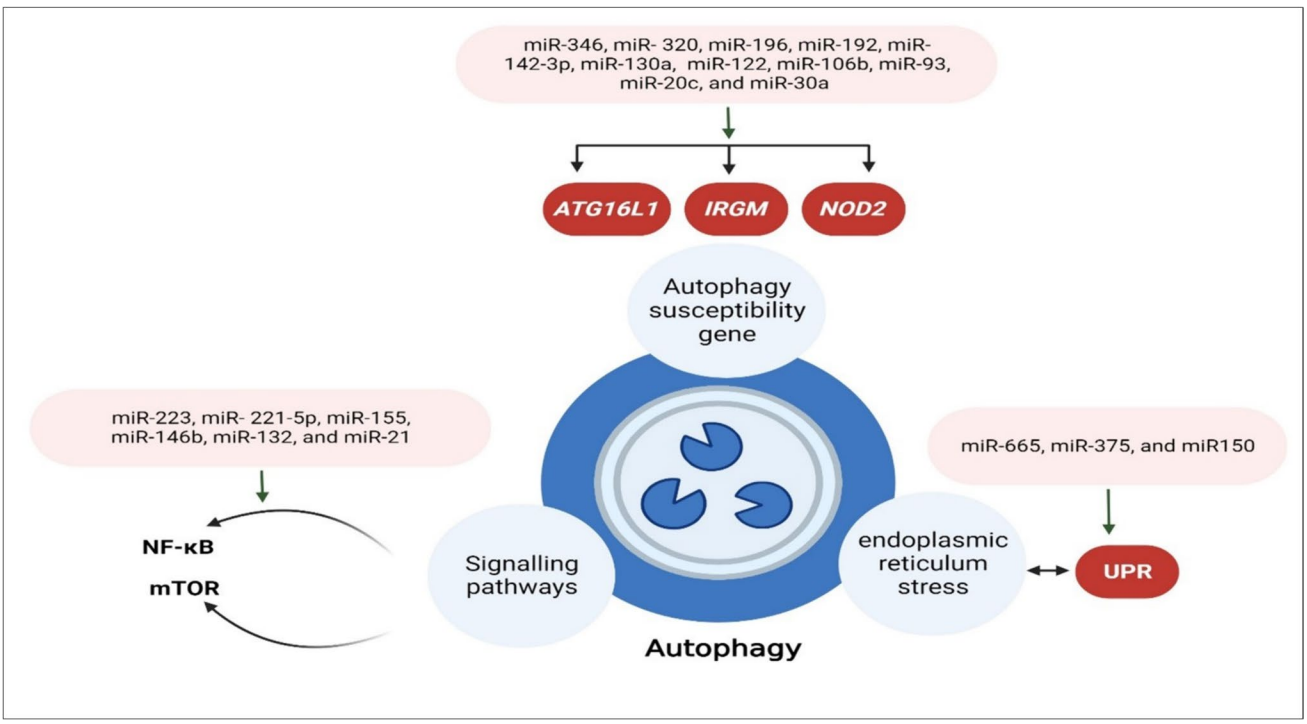

Fig. 4 miRNAs influence cell autophagy during IBD via several molecular pathways. a miRNAs interact with autophagy genes associated with IBD, including *ATG16L1*, *IRGM*, and *NOD2*, to modify intestinal barrier integrity and innate intestinal immunity. **b** miRNAs regulate autophagy via modifying the unfolded protein response (UPR) during endoplasmic reticulum stress, which causes intestinal fibrosis in IBD patients. **c** miRNAs modulate NF-κB and mTOR signaling pathways that influence inflammatory mediators and intestinal autophagy. **Created with BioRender.com**

and turnover were increased upon deletion of IEC-specific miR-802 in mice models. This is due to the binding of miR-802 to its target, Tmed9, which promotes defensin and Wnt secretion from Paneth cells [76].

Intestinal membrane disruption is a major contributor to the pathophysiology of IBD. It is well recognized that a key pro-inflammatory cytokine in the etiology of IBD is TNF-α. So, several in vitro studies have been carried out employing intestinal epithelial cells to cause TNF-α-induced damage [90]. It is well established that miR-191a [91] and miR-212 [92] erode IB integrity. Indeed, in vitro investigations have demonstrated that their mimics suppress the production of zonula occludens (ZO)-1, which is a key element of the tight junction connecting the IEC. Zou et al. [93] measured the interaction of miR-675 in colon cells in vitro and discovered that miR-675 destabilized the ZO-1 and E-cadherin mRNA, resulting in decreased production of vital proteins for intercellular tight junctions. Aquaporin 3 (AQP3) is an additional essential protein in IB. According to Zhi et al., [94] miR-874 increases paracellular permeability in vitro by downregulating the AQP3 protein via targeting its 3'UTR.

These findings, taken together, suggest candidate miRNAs that could be targeted to preserve IEC-mediated gut homeostasis, regulate tight junctions, and support barrier function in different GIT disorders such as IBD.

miRNAs and gut microbiota

Interestingly, miRNA and microbiota interact reciprocally. Although exciting research on miRNAs has increased greatly in recent years, pointing to these tiny molecules as key players in the host-microbiota connection, the precise mechanisms by which miRNAs are implicated in IBD or dysbiosis remain unknown. On one hand, host miRNA may play an important role in IBD pathogenesis by modulating the gut microbiota. Conversely, the gut microbiota may influence the expression of host miRNAs, leading to intestinal epithelial disruption, impaired autophagy, and immunological hyperactivation [20, 95, 96].

In 2011, Dalmasso et al. [97] reported one of the first proof of this interaction. They investigated the effects of introducing the microbiota of pathogen-free mice into germ-free mice. Such colonization resulted in differential expression of miRNA and host genes in both the ileum and the colon. Then, Nguyen et al. [98] studied the mechanism by which some pathogenic bacteria such as adherent-invasive *Escherichia coli* (AIEC) alter the expression of miRNAs in CD patients. They found that AIEC infection increases the expression of miR 30C and miR130A, which reduces the expression of autophagy proteins (ATG5 and ATG16L1) and inhibits autophagy, resulting in an increase in intracellular AIEC and an inflammatory response. Additionally, Viennois et al. [99] reported that the gut microbiota influences fecal miRNAs such as let-7, miR-148, miR-21, and miR-196, whose levels are connected with the microbiota composition and inflammatory potential. Similarly, Tomkovich et al. [100] descried the relationship between fecal miRNAs and the abundance of particular bacterial taxon. They found that some of these miRNAs affected host genes and others affected bacterial genes, demonstrating a complex bacteria-miRNA-host connection. Furthermore, Johnston et al. [101] demonstrated that miR-21 expression boosts intestinal inflammation after altering the composition of the intestinal microbiota. They also established that the absence of miR-21 protects from colitis by decreasing Bacteroidetes and increasing protective Firmicutes and *Clostridia*.

Thus, miRNAs could serve as therapeutic agents (through mimicking or blocking approaches), acting on the host and/or the gut microbiota to manage IBD patients. Furthermore, diets enriched with prebiotics or probiotics should be considered, as they may help in altering the intestinal microbiota and regulating miRNA expression, to alleviate the intestinal inflammatory process in IBD patients. All of these approaches, however, require additional research and study in order to be properly understood and applied in the future.

miRNAs and differential diagnosis of IBD

In 2008, the first miRNA fingerprinting study of IBD was conducted. Biopsy samples from patients with irritable bowel syndrome (IBS), microscopic colitis, infectious colitis, chronic active CD (aCD), active UC (aUC), and inactive UC (iUC) were compared with those from healthy controls [102]. Patients with aUC had differing expression levels of 11 miRNAs than the control group. miR-16-5p, miR-21-5p, miR-23a-5p, miR-24-3p, miR-29a-3p, miR-126-3p, miR-195-5p, and let-7f-5p were substantially elevated, while miR-192-5p, miR-375-3p, and miR-422b-5p were dramatically decreased. Later, several investigations were carried out to describe these changes in miRNA expression [103–105], and as a result, a number of these miRNAs were proposed as putative markers for UC and CD in colon biopsies as well as non-invasive samples including blood, feces and saliva [13, 14, 106–108]. In individuals with active colonic or ileal CD, differential miRNA expression was seen in tissues from various intestinal sites. In comparison to the colon, the terminal ileum showed upregulation in miR-22, miR-31, and miR-215 and downregulation in miR-19b, indicating that unique inflammation-related gene expression in each IBD subtype may be modulated by miRNAs [105].

It should be highlighted that several parameters vary between studies, including medication, inflammatory condition, disease duration, anatomical biopsy sites,

various healthy control groups, and miRNA profiling technologies, therefore the results may be inconsistent and confusing.

The most significantly differentially expressed miRNAs

In order to develop miRNA-based new diagnostics and therapies for IBD, it is critical to understand how miRNA expression variations correlate with disease type, the underlying processes that control miRNAs, the targeted genes, and their interaction. Regardless of the variability of miRNAs that are differentially expressed in IBD, 66 miRNAs were found by literature and meta-analysis to be significant candidates for therapeutic or diagnostic uses [109]. In the next section, we will focus on miRNAs that have been experimentally observed to particularly target IBD-related genes [110, 111].

Proinflammatory miRNA

Let-7i-5p

Let-7i-5p is a regulator of IL-6 and toll-like receptor 4 (TLR4), both of which are crucial for cytokine-mediated responses [112]. TLR4 mRNA and protein levels were downregulated in the THP-1 cell line transfected with let-7i-5p mimics [113]. In allergic inflammation, Let-7i-5p appears to help cells reset their protein composition in response to outside stimuli, however, the precise process is yet unknown [114]. Let-7i-5p functions as a major regulator of inflammation, fibrosis, hypertrophy, and cell death via controlling collagens, IL-6, IGF-1, caspase-3, and TGF-βR1 [112].

miR-16

miR-16 may have a role in the regulation of the NF-κB pathway UC by targeting the mRNA of the adenosine A2a receptor (A2aAR), NF-κB inhibitor. At the post-transcriptional level, miR-16 inversely controlled the expression of A2aAR. Moreover, colonic epithelial cells transfected with miR-16 mimics expressed pro-inflammatory cytokines, such as IFN-γ and IL-8, and nuclear translocation of NF-κB p65 protein. These harmful effects could be reversed by treating the cell with anti-miR-16 [115].

miR-19a-3p and miR-19b-3p

MiR-19a-3p and miR-19b-3p were identified as putative pathogenic indicators by serum miRNA screening of CD patients with and without strictures. Decreased levels of miR-19a-3p and miR-19b-3p were shown to be substantially associated with CD patients developing strictures, regardless of location, age, gender, illness duration, or activity [116]. Furthermore, it has been documented that miR-19a-3p increases IFN-α and IL-6 signal transduction by reducing Suppressors of cytokine signaling 3 (SOCS3) expression [117].

miR-21-5p

miR-21-5p was demonstrated to have a critical role in cytokine modulation [118], adaptive immune responses [119], colon epithelial cell hemostasis [120], as well as complications associated with IBD [121, 122]. Additionally, it has been shown that miR-21-5p increases intestinal permeability as a consequence of epithelial injury. When miR-21-5p mimics were transfected in the UC mouse mode, tight junction proteins were lost, barrier permeability increased [120], and the number of $CD3^+$ and $CD68^+$ cells dropped [15]. The knockout of miR-21-5p in mice models also demonstrated strong resistance to colitis produced by DSS, indicating that this miRNA has pro-apoptotic properties [15]. miR-21-5p plays a role in TLR4 stimulation and monocyte differentiation and possesses a regulatory function in innate immunity. Additionally, danger signals—such as NF-kB activators in a negative feedback loop—induce miR-21-5p in order to stop damage [123]. Furthermore, via targeting the IL-12p35 receptor, this miRNA controls the release of IL-12 from macrophages and dendritic cells [118]. miR-21-5p was also shown to have an important role in T-cell activity, with the greatest detectable expression in effector and memory T-cells and the lowest in naïve T cells [102]. However, this miRNA may be linked to permanent IBD fibrosis, and serum levels of it are elevated in patients with severe fibrosis and dysplasia [124, 125]. It is important to note that various cellular damage models have been demonstrated to be TNF-dependent, with concurrent miR-21-5p upregulation [29].

miR-24-3p

It has been found that miR-24-3p influences T cell development, proliferation, and immunological responses [126]. Additionally, it has been discovered that miR-24-3p silences pro-survival genes such as *PAK4* and *Bcl-2* which results in cell death [127]. PMS2L2 overexpression induces methylation of the miR-24-3p gene, which inhibits it and inhibits cell apoptosis in UC. PMS2L2 overexpression, in response to LPS, has been demonstrated to enhance *Bcl-2* expression while inhibiting cleaved-caspase-3, cleaved-caspase-9 production, and Bax expression [128]. Moreover, via targeting furin, miR-24-3p modulates the pathway of latent TGF-1 release [129].

miR-29a-3p

miR-29a has a role in the pathophysiology of UC by influencing intestinal epithelial cell apoptosis through *Mcl-1*. The 3'UTR of the *MCL-1* gene contains a seven-nucleotide broad binding site for miR-29a-3p [130]. It has been demonstrated that overexpression of miR-29a-3p in colonic tissue results in increased intestinal membrane permeability. On the other hand, it has been found that miR-29a-39 targets LPL in ox LDL-stimulated dendritic cells to control the expression of scavenger receptors and the release of pro-inflammatory cytokines [131].

miR-30c-5p

Nguyen et al. showed that adherent-invasive *Escherichia coli* (AIEC) infection, which colonizes the ileal mucosa of CD patients, upregulates the expression of miR-30c-5p in T84 cells through nuclear factor-κB activation. Up-regulation of this microRNA decreases the level of Autophagy related 5 (ATG5) protein and hence hinders autophagy, resulting in a surge in the number of intracellular AIEC and severe inflammatory response [98]. The author documented the same effect in both human patients and mouse models. On the other hand, it is thought that miR-30c-5p regulates the differentiation of Th17 cells by targeting its negative regulators, including TGFβR2, SOCS3, FOXO3, TSC1, SMAD2, as well as SMAD4 [132]. Therefore, the number of Th17 cells may rise or fall as a result of their differential regulation. Other significant targets of miR-30c-5p include STAT1, ETS1, and BCL6.

miR-31-5p

MiR-31-5p was shown to target FIH-1, an inhibitor of Hypoxia-inducible factor 1 (HIF-1) protein, and demonstrated a progressive increase from normal to IBD conditions [133]. Furthermore, it has been demonstrated that suppression of miR-31-5p in keratinocytes in psoriasis suppresses NF-κB-driven promoter-luciferase activity and IL-1β, CXCL1, and CXCL5 production [134]. miR-31-5p uses STK40 as its main target to attract leukocytes and control the production of these cytokines and chemokines in endothelial cells. Additionally, by targeting and inhibiting retinoic acid-inducible protein 3 (Gprc5a), miR-315p adversely controls the production of peripherally derived Treg cells [135]. In this regard, deletion of miR-31-5p boosts this Treg cell induction and minimizes the severity of EAE in animal models. IL-13 is a vital Th2 cytokine that regulates epithelial function by binding to the IL-13 receptor A1 (IL13RA1). Gwiggner et al. [136] discovered that miR-31 and miR-155 levels are elevated in inflamed UC mucosa and both target the 3' UTR of IL13RA1. In the gut epithelial cell line, transfection of miR-31 and miR-155 mimics decreased the expression of IL13RA1 mRNA and protein, inhibited IL-13-dependent phosphorylation of STAT6, and decreased the expression of SOCS1 and CCL26. These results may exacerbate the disease condition [136]. Moreover, post-ablation epithelium with higher barrier permeability had a variable expression of miR-31-5p [137]. Most recently, Qu et al. [138] proposed that miR-31 inhibition on cytokine receptors is important for controlling inflammation and may be used as a beneficial target for developing new drugs.

miR-106a-5p

In both CD and UC patients, serum miR-106a-5p levels are correlated with the severity of the disease [139]. It has been demonstrated that miR-106a-5p is upregulated through T-cell activation, although the majority of miRNAs are downregulated [140]. Moreover, miR-106a-5p in macrophages can control signal regulatory protein α (SIRPα) production and, thus, SIRPα-mediated inflammation [141]. Several studies demonstrated the effect of miR-106a-5p on IBD prognosis in both human and animal models [58, 142, 143]. By using the dual-luciferase reporter (DLR) assay, Li et al. [142] found that STAT3 is a target gene of miRNA-106a-5p. Therefore, miRNA-374b-5p and miRNA-106a-5p possess a role in IBD pathogenesis by regulating IL-10/STAT3 signaling pathway. Furthermore, Sanctuary et al. [58] found that miR-106a-5p knockout can ameliorate chronic ileitis in murine models and boost the suppressive function of Treg cells. It was demonstrated that a deletion in miR-106a-5p will enhance Treg induction and IL-10 production, and attenuate colitis in T cell-restricted deficiency [144]. Under physiological settings, TGFβ seems to reduce miR-106a in order to improve Treg induction. Under inflammatory circumstances, TNF-α tends to cause overexpression of miR-106a-5p via NF-B-dependent activation of the miR-106a-5p promoter, leading to transient repression of normal immune control [58].

miR-142-5p and miR-142-3p

miR-142-5p is the most common isoform in thymically Tregs [145]. MiR-142-5p has been demonstrated to negatively regulate PD-L1 expression by targeting its 3-UTR [146]. It has been demonstrated that overexpression of miR-142-5p causes the upregulation of proinflammatory TNF-α and IFN-γ and the downregulation of anti-inflammatory IL-10 [109]. Han et al. [147] reported that colonic mucosa of UC patients as well as HT-29 cell lines treated with TNF-α experienced downregulation of long non-coding RNA TUG1, which is considered a negative regulator of miR-142-5p. Thus, upregulation of miR-142-5p abolishes TUG1-mediated suppression of TNF-α induced IL-6, IL-8, and IL-1β.

Moreover, Xiang et al. [148] demonstrated that miR-142-5p negatively regulates the protective circular RNA CCND1. Furthermore, miR-142-5p was reported to be substantially expressed in UC, and its knockdown prevented inflammatory reactions and Caco-2 cell death triggered by LPS. Additionally, miR-142-5p was demonstrated to enhance intestinal inflammation in aUC patients by upregulating the expression of the suppressor of cytokine signaling 1 (SOCS1) and secreting more IL-6 and IL-8 cytokines [149]. Duijvis et al. [150] discovered that inhibiting miR-142-5p ameliorates colitis in animal models, potentially via activating the Interleukin-10 receptor subunit alpha (IL10RA) pathway. Moreover, miR-142-5p specifically targets and inhibits genes that encode tight junction proteins (TJPs), such as TJP1, occludin, and claudin-8 [151].

MiR-142-3p is expected to target ATG16L1, one of the most frequently found genetic variants in CD patients. It has been reported that ATG16L1 in colonic epithelial cells of CD patients is negatively regulated by miR-142-3p. Thus, upregulation of miR-142-3p decreased the expression of ATG16L1, which in turn decreased the autophagic capacity of thymic-derived Tregs. According to Li et al., [152] miR-142-3p can inhibit the stimulation of the ERK1/2 signaling pathway through downregulating *RAC1* expression, which results in a Treg function deficiency. Additionally, it has been demonstrated that miR-142-3p antagomir can impact the apoptosis, and cytokine production, as well as the regulatory function of induced Treg cells via Foxp3 expression [153].

miR-150-5p

miR-150-5p is thought to play a role in IBD. In IBD, miR-150-5p was reported to be upregulated [154, 155]. miR-150-5p targets c-Myb, which is markedly downregulated in the colons of UC patients and the colitis model. Thus, it has been observed that overexpression of miR-150-5p increases the damage to intestinal barrier by targeting c-Myb [156]. In this regard, Rodríguez et al. [157] observed that the *Lactobacillus fermentum* probiotic can improve dysbiosis alter the level of miR-150-5p, and restore intestinal integrity and permeability. In addition, Ishihara et al. [155] found that miR-150 knockdown stopped the proliferation of damaging Th17 cells and the onset of colitis, suggesting that miRNA may considered as a potential therapeutic target for the management of IBD.

miR-155-5p

miR-155-5p is a well-known proinflammatory, oncogenic miRNA that is significantly expressed in activated T and B cells in addition to macrophages. miR-155-5p is essential for a functioning immune system as it regulates the activity of DCs and lymphocytes. In GIT, aberrant miR-155 expression has been reported in several disease conditions such as IBD and CRC [158]. Previous research indicated that miR-155 is upregulated in different sample types of IBD patients [159]. Expression of miR-155-5p is elevated in antigen-presenting cells (APCs), such as macrophages and DCs, in response to inflammatory mediators such as LPS, TLR ligands, and IFN-β. Additionally, it has been discovered that antigen-stimulated T and B lymphocytes trigger the expression of miR-155-5p [156]. Furthermore, one of the primary targets of miR-155-5p is SOCS1, which is a negative regulator for the triggering of LPS-induced macrophage, antigen presentation by DCs, and JAK/STAT signal pathway [160]. In addition, miR-155 antagomir protects mice from DSS-induced colitis via modulating Th17/Treg cell balance [161].

miR-199a-5p

miR-199a-5p was found to be significantly elevated in the blood of aUC and aCD patients compared to healthy controls [162]. miR-199a-5p was investigated to possess a pro-inflammatory effect. Overexpression of miR-199a-5p induces the phosphorylation of STAT 1 and STAT 3 proteins [163]. miR-199a-5p was shown to be implicated in endoplasmic reticulum stress (ERS) and cell death in vitro, and its overexpression promoted ERS, weight loss, apoptosis, and UC in vivo. Wang et al. [164] demonstrated that these effects might be avoided by inhibiting miR-199a-5p.

miR-223-3p

miR-223-3p was reported to be upregulated in feces and colonic biopsies of aUC and aCD [14, 165, 166]. Schönauen et al. [106] reported that the feces of active UC patients had miR-223 elevated by over 67-fold. Furthermore, Wang et al. observed that in CD patients, miR-223 had a stronger correlation with disease activity than high-sensitivity C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR). miR-223-3p is overexpressed in naïve CD4 + T-lymphocytes and has been implicated in the stimulation of granulocytes. miR-223-3p enhances the development of IBD by suppressing the expression of TJP, claudin 8 [84]. Further in vivo study found that miR-223 is a key mediator in the communication between the IL-23 pathway through targeting claudin 8 and administration of its antagomir to restore claudin 8 level, improve intestinal barrier, and ameliorate DD-induced colitis [14]. Conversely, Zhang et al. [167] found that, in DSS-induced colitis mice, miR-223 agomir led to the downregulation of Bcl-2 and Bcl-xl as well as an alleviation of colonic inflammation through inhibiting IL-6/STAT3 pathway.

miR-424-5p

It's been demonstrated that miR-424-5p regulates monocyte/macrophage development. PU.1 is the transcription factor that controls the increase of miR-424-5p expression. MiR-424-5p, when activated, stimulates monocyte differentiation by inhibiting NFI-A [168]. Coll et al. [169] discovered that miR-424-5p possesses pro-angiogenic properties and promotes the expression of genes involved in vessel creation and the remodeling of the vascular compartment in CD stenotic and penetrating lesions, thus promoting the progression of CRC [170].

Anti-inflammatory miRNA

miR-23b-3p

miR-23b-3p suppresses inflammatory cytokine production and NF-κB activation generated by (IL-17, IL-1β, and TNF-α,) by targeting TGF-β-activated kinase 1/MAP3K7 binding protein 2 (TAB2), TAB3, and inhibiting NF-κB kinase subunit α. This effectively suppresses autoimmune inflammation. In contrast, IL-17 promotes autoimmune inflammation by inhibiting miR-23b-3p production and increasing proinflammatory cytokine production [171].

miR-28-5p

The functions of miR-28-5p have been demonstrated to include cell invasion, migration, proliferation, and the epithelial-to-mesenchymal transition (EMT) [172]. miR-28-5p has the ability to suppress programmed cell death protein 1 (*PD1*) genes while also regulating PD1 + Foxp3 + and TIM3 + Foxp3 + exhaustive Treg cells [173].

miR-30d-5p

miR-30d-5p has been demonstrated to control lactase expression and boosts the amount of *Akkermansia muciniphila* in the gut. As a result, *Akkermansia* raises Tregs to reduce symptoms of EAE. Furthermore, oral administration of miR-30d-5p mimic decreases experimental EAE [174].

miR-126-3p

Few studies established that miR-126-3p may contribute to the inflammatory process and IBD pathogenesis [175], whereas other studies demonstrated that miR-126-3p may possess an anti-inflammatory effect [176–178]. Active UC tissues have been demonstrated to exhibit a noticeable decrease in IκBα, the NF-κB inhibitor. Feng et al. demonstrated that miR-126-3p, by binding to the 3′-UTR of IκBα that inhibits the NF-κB signaling pathway, plays a role in the pathogenesis of UC [175]. Conversely, Zou et al. [178] demonstrated that miR-126-3p mimics can attenuate multiple organ dysfunction through upregulation of Treg and downregulation of Th17. Furthermore, it has been shown that miR-126-3p inhibits the expression of vascular cell adhesion molecule 1 (VCAM-1), which is involved in leukocyte adherence to endothelial cells, increasing the recruitment of immune cells and aggravating inflammation [176, 179]. Most recently, Jiang et al. [180] showed that miR-126-3p not only inhibits VCAM-1 expression but also IL-1β. MiR-126-3p suppression has been observed to increase PIK3R2 expression in CD8 + T cells and modify the PI3K/Akt pathway activation, which is crucial for induction and suppressive functions of Treg cells [181].

miR-140-5p

miR-140-5p has been demonstrated to be downregulated in various inflammatory conditions [182–186]. Numerous miR-140-5p targets control proliferation, cell cycle, and apoptosis of cells [184]. According to research, miR-140-5p downregulates TLR-4 through direct binding of its 3′-UTR and thus prevents the release of pro-inflammatory cytokines. Furthermore, miR-140-5p has been shown to suppress IL-6 and IL-8 production via modulating TLR-4 expression [182]. Yang et al. [187] observed that downregulation of miR-140-5p elevate the level of pro-inflammatory cytokines such as IL-1β, IL-6, and TNF-α in addition to upregulation of TLR-4/NF-κB signaling pathway in an in vitro model.

miR-141-3p

IBD and other autoimmune disorders, such as lupus and psoriasis, are characterized by abnormal expression of miR-141-3p [188, 189]. CXCL12β, a chemokine produced by epithelial cells that control colonic leukocytic trafficking, has been demonstrated as the target of miR-141-3p. Additionally, the CXCL12β is inversely correlated to miR-141-3p. Thus, it is hypothesized that miR-141-3p's targeting of CXCL12β may affect the trafficking of inflammatory cells toward inflammatory areas. Therefore, preventing immune cell trafficking and suppressing colonic CXCL12β expression may be beneficial for treating CD [190]. Additionally, miR-141-3p has been shown to inhibit STAT4, subsequently preventing inflammatory mediators [191]. Shen et al. [192] demonstrated that miR-141-3p upregulation attenuates the intensity of chronic inflammatory pain by downregulating downstream target gene high-mobility group box1 (*HMGB1*), which in turn lowers the levels of IL-1β, IL-6, and TNF-α. Chen et al. [193] also showed that elevated expression of miR-141-3p may ameliorate the necrotizing enterocolitis by targeting the motor neuron and pancreas

homeobox 1 (*MNX1*) gene, which controls the expression of oxidative stress markers such as (SOD, MPO, and MDA) and inflammatory mediators such as (IL-1β, IL-6, and TNF-α). Furthermore, miR-141-3p was found to ameliorate intestinal epithelial cell damage caused by LPS via suppressing necroptosis and inflammation mediated by receptor-interacting protein kinase 1 (*RIPK1*) [194]. Most recently, Yan et al. [195] reported that, through targeting SUGT1, miR-141-3p may also prevent colonic epithelial cell pyroptosis caused by LPS. miR-141-3p may also reduce DSS-induced UC in mice. This suggests that miR-141-3p might be developed into a nucleic acid medication for the management of UC.

miR-146

miR-146a-5p has been demonstrated to control the innate immune reactions and TNF-α cascade in skin inflammation [196]. miR-146a-5p lacking mice also experience immune system problems [197]. This miRNA controls NOD2-derived gut inflammation and reduces proinflammatory cytokines produced by activated macrophages in IBD patients [198]. miR-146a expression is triggered immediately by NF-κB binding to its promoter [199]. Consequently, elevated miR-146a suppresses TLR signaling by going after TNF receptor-associated factor 6 (TRAF6) and interleukin-1 receptor-associated kinase 1 (IRAK-1). This lowers the inflammatory mediators, IL-1β, IL-6, and TNF-α, in infected macrophages [200]. Similarly, in human intestinal epithelial cells, miR-146a-5p downregulates the IRAK1/TRAF6 signaling pathway, which in turn adversely controls the IL-1β-stimulated inflammation. As a result, miR-146a-5p could be a crucial indicator for diagnosis and a therapeutic target for IBD [201]. Additionally, in the experimental colitis model, miR-146a also targets receptor-interacting serine/threonine kinase 2 (RIPK2), a NOD-like receptor signaling mediator and restricts the secretion of Th17-driving cytokines from intestinal dendritic cells (DCs) and macrophages, including IL-1β, IL-6, and IL-23 [202]. Furthermore, in response to LPS, overexpression of miR-146a-5p in monocytes led to reduced levels of TLR4 signaling network downstream genes [203].

miR-146b-5p has also been reported to be downregulated in IBD and LPS-induced macrophages. miR-146b directly targets and downregulates fibrinogen Like 2 (*FGL2*) gene. Therefore, by suppressing *FGL2*-activated NF-κB/MAPK signaling pathway, miR-146b alleviates intestinal inflammation in vivo and prevents M1 macrophage polarization in vitro [49]. On the other hand, miR-146b-5p may reduce intestinal inflammation via increasing NF-κB expression as a consequence of reduced levels of the *siah2* gene, which ubiquitinates TNF receptor-related factor proteins. In turn, activation of NF-κB cascade promotes intestinal epithelial function, suppresses autophagy, decreases intestinal inflammation in DDS-induced colitis, and raises the survival rate [48]. The most recent Egyptian study demonstrated that the expression of miR-146b-5p significantly increased in CD patients compared to UC, and its expression in patient's serum increased with disease activity [143].

miR-146b-3p, an additional member in the miR-146 family, has been demonstrated to hinder TNF-α release, inhibit proinflammatory adenosine deaminase 2 (ADA2) [204]. Moreover, elevated STAT3 activity dramatically downregulates the expression of miRNA-146b-3p [205].

miR-149-5p

miR-149-5p has been demonstrated to be downregulated in IBD. Wu et al. [162] found that miR-149-5p was differentially expressed in UC and CD. miR-149-5p expression was significantly decreased in aUC patients. miR-149-5p has been demonstrated to suppress TLR-induced inflammatory cytokine production by targeting MyD88. Similarly, Luo et al. [206] reported that both miR-149 isoforms (miR-149-5p and miR-149-3p) were downregulated in IBD and may linked to the disease activity. These findings thus point to their significance as disease monitoring biomarkers. Recent research using in vitro and in vivo models of colorectal cancer (CRC) and IBD revealed that the Enterotoxigenic *Bacteroides fragilis* (ETBF) bacteria, which is closely linked to these two illnesses, adversely regulates miR-149-3p which is crucial for suppressing tumor cells [207]. Furthermore, Feng et al. [208] discovered that miR-149-3p deletion alters gut microbiome and enhances the pathogenesis of DDS-induced colitis in mice.

miR-192-5p

miR-192-5p was downregulated in both UC [102, 209] and CD [166, 210]. According to one study, miRNAs have important roles in CD etiology and inflammatory modulation, comparable to UC. miR-192 was shown to lower inflammatory activation by suppressing NOD2 receptor function in colonocytes [210]. On the other hand, the downregulation of miR-192 might impact the progression of CD by over-activating NOD2 through muramyl dipeptide. It has been demonstrated that miR-192-5p targets and negatively regulates macrophage inflammatory Peptide 2 Alpha (*MIP2α*) (CXCL2), a CXC chemokine that is produced by epithelial cells and is crucial for both human and mouse IBD. A miR-192-5p analogue has been shown to decrease *MIP2α* expression [102]. Furthermore, miR-192-5p controls the expression of collagen and chemokines, both of which are essential for fibrosis and inflammation [25].

miR-195-5p

There is a correlation between the severity of IBD and miR-195-5p level. A previous study documented that miR-195-5p is overexpressed in UC patients [102]. It has been demonstrated that overexpressing miR-195-5p decreases M1 macrophage polarization. When miR-195-5p was overexpressed, TLR2 levels in M1 macrophages activated by LPS and IFN-γ decreased. Moreover, miR-195-5p dramatically reduced the levels of TNF-α, IL-6, and IL-1β in cultures of M1-stimulated macrophage supernatant. Overall, miR-195-5p appears to be involved in the polarization of macrophages through the inhibition of TLR2 inflammatory pathway regulators [211].

miR-200 family

miR-200 family includes miR-200a, b and c. It has been demonstrated that miR-200b was downregulated in colonic biopsies from both UC and CD. However, miR-200a and miR-200c were downregulated in colonic biopsies of CD [212]. It is believed that the pool of activated fibroblasts in IBD fibrosis is influenced by the epithelial-to-mesenchymal transition (EMT). Typically, the miR-200 family of miRNAs inhibits the production of EMTs [212]. Multiple studies, however, found that miR-200b had a greater anti-EMT effect than miR-200a and miR-200c [212–215]. An in vitro study found that miR-200b maintains intestinal epithelium integrity by suppressing EMT and enhancing IEC proliferation [213]. Another study found that *Clostridium butyricum* restored intestinal epithelium integrity by boosting miR-200c expression [216]. Furthermore, the intestinal epithelial barrier is shielded by over-expression of miR-200b, which suppresses the TNF-α-upregulated JNK/c-Jun/AP-1 signal and IL-8 production in Caco-2 cells [217]. miR-200c-3p suppresses NF-κB inflammatory pathway in response to LPS-induced TLR4 activation [218].

miR-375-3p

miR-375-3p is downregulated in aUC [102] and aCD [105, 108, 166] patients' intestinal mucosa and feces. However, it was reported to be upregulated in the peripheral blood of UC and CD patients compared to the control [108]. Alam et al. [219] concluded that the downregulation of miR-375 in colon tissues may be directly related to less targeted regulation of CTGF-EGFR, with consequent elevated tissue proliferation influencing cancer progress. miR-375-3p was reported to competitively suppress the expression of TLR-4. In LPS-induced caco-2 cells, knocking down miR-375 might trigger pro-inflammatory cytokines production such as IL-1β, IL-6, IL-8, and TNF-α, and deterioration of intestinal integrity [16]. Furthermore, Cheng et al. [220] observed that miR-375-3p reduces the intensity of inflammation by targeting YAP1/LEKTI pathway.

miR-378a-3p

miR-378a-3p is downregulated in aUC [221] and feces of CD [166]. miR-378a-3p has been demonstrated to target and negatively regulate IL-33 [221]. Li et al. [222] showed that mesenchymal stem cells-derived extracellular vesicles (MSCs-EVs) carrying miR-378a-3p can inhibit the GATA2/AQP4/PPAR-α pathway, therefore decreasing LPS-induced apoptosis in M064 cells and preventing the development of IBD. The miR-378a-3p is found in intron 1 of the *PPARGC1B* gene, which is regulated differently in the intestinal mucosa of UC patients [223]. *PPARGC1B* protein is abundantly expressed in the intestinal epithelium and has a role in energy generation and biogenesis [224], regulation of mitogenesis, and mitochondrial metabolism [225]. Consequently, it can be said that in inflammatory mucosa, the reduction in miR-378a-3p may indicate a metabolic change, perhaps connected to an increase in energy consumption and the overproduction of ROS [226].

miR-532-3p

miR-532-3p was downregulated in the peripheral blood of aUC [102] and aCD [162]. miR-532-3p suppresses inflammation by inhibiting the ASK1/p38 MAPK signaling cascade in LPS/TNF-stimulated macrophages. For this reason, it has been proposed as a possible target for the treatment of inflammatory autoimmune disorders like IBD [227].

In summary, numerous miRNAs have been found since their discovery. There is growing evidence that certain miRNA expression profiles have a role in the onset and progression of IBD. The majority of studies find correlations rather than causal links between IBD and differentially expressed miRNAs. The exact role of the majority of miRNAs in IBD remains unclear since, as was previously said, very little research focuses on the underlying biological processes of the illness. Additionally, a lack of standardized study designs and varied methodologies have contributed to the lack of consistency between investigations.

We concluded that there are common miRNAs (such as miR-16, 21, 31, 155, and 223) as well as some differentially expressed miRNAs in colon biopsies, peripheral blood, feces, and saliva after comparing miRNAs in various tissues among UC or CD patients and control. These differentially expressed miRNAs may aid in the clinical diagnosis and differentiation of UC and CD. Furthermore, it is unlikely that the miRNA expression seen in colon biopsies will match the miRNA expression in peripheral blood, as that present in blood might represent expression in circulating white blood cells (WBCs) [25]. The varying evolutionary stages of IBD

may also contribute to variations in the expression level of miRNA. (Table 1) and (Table 2) clarifies the differentially expressed miRNA across various sample types in UC and CD, respectively.

miRNAs as a target for the treatment of IBD

Preclinical animal studies

In the future, miRNAs could serve as the real therapeutic target in addition to their function as diagnostic markers and indicators of inflammatory activity [228]. Several miRNAs have been found to work on similar inflammatory pathways as some biological drugs that are approved for the management of IBD. miR-29 has been found to be a member of the miRNA family capable of downregulating pro-inflammatory IL-23, similar to Ustekinumab, a monoclonal antibody that suppresses IL12/23. Therefore, mimicking miR-29 is advised in moderate to severe CD cases. [46, 176]. miR-126 prevents leukocyte adherence to endothelial cells via regulating VCAM-1, which is a comparable mechanism of action with vedolizumab, which is additionally approved for the management of IBD [176, 229]. The miR-155 antagomir targets and negatively regulates a JAK signaling pathway regulatory protein [230], simulating the usage of JAK inhibitors presently available for the management of UC [231].

miRNAs have a specific way of action, which suggests that either blocking or increasing miRNA expression may be preferable in order to alleviate IBD. Lima et al. have provided a detailed introduction to gain-of-function strategies like using chemically generated miRNA mimics or agomirs, and loss-of-function strategies like using miRNA sponge technology or using miRNA antagomir [232].

Up till now, these two approaches have shown promising results in preclinical animal models of IBD as well as in vitro cell lines, however, clinical data is lacking. For example, the enema administration of leptosome-miR31 mimics packed into oxidized konjac glucomannan, in the DSS-induced miR-31 knockout mice model, results in an inhibition of inflammatory reaction, increases body weight and colon length, as well as promotes epithelial cell proliferation in contrast to controls [79]. While miR-31 is elevated in the clinic, it is still unknown if this slows down or speeds up the development of IBD [79]. Moreover, numerous miRNA inhibitors have been reported to upregulate the expression of TJ protein in the UC or CD animal models, including antisense miR-122a, miR-7a-5p antagomir, miR-155 antagomir, and miR-223 antagomir [14, 233–235]. According to Fang et al., miR-31-3p agomir reduced the severity of colitis produced by DSS in mice via downregulating RhoA [236].

Additionally, apoptotic genes also appear to be attractive candidates for miRNA modulation in the management of IBD. *Bcl-2* and *Bcl-XL* are known to have an anti-apoptotic effect. In this context, Chen et al. [237] reported that intraperitoneal injection of miR-16 antagomir increased the expression of *Bcl-2* and improved intestinal function in the DSS mice model. On the other hand, Zhang et al. [167] found that in the DSS mice model, miR-223 agomir led to the downregulation of *Bcl-2* and *Bcl-xl* with subsequent remission of colonic inflammation. Remarkably, miR-223 has been identified as a pro-inflammatory miRNA in several investigations [14, 238]. Therefore, further research is needed to resolve this confusion. Furthermore, additional strategies to enhance the effectiveness of miRNA in vivo administration are being investigated by researchers. According to Suri et al., [107] there are five primary methods for delivering miRNA: viral vectors, exosomes, and conjugates in addition to lipid carriers (like lipid nanoparticles and

Table 1 Differentially expressed miRNA across various sample types in UC [159, 257]

Sample type	Upregulated miRNA	Downregulated miRNA	References
Peripheral blood	miR-16, miR19a, miR-21, miR-28-5p, miR-30e, miR-101, miR-103-2, miR-106, miR-142-5p, miR-146-5p, miR-151-5p, miR-155, miR-199a-5p, miR-215, miR-223, miR-340, miR-362-3p, miR-374b, miR-375, miR-494, miR-532-3p, miR-598, miR-638, miR-642, and miRplus-E1271	miR-21, miR-31, miR-146a, and miR-505	[108, 139, 162, 258–260]
Feces	miR-16-5p, miR-21-5p, miR-126, miR-155, miR-203, miR-223, and miR-1246	miR-192 and miR-320	[106, 121, 165, 209]
Saliva	miR-21, miR-31, and miR-142-3p	miR-142-5p	[108]
Intestinal biopsy	miR-15, miR-16-5p, miR-19a, miR-21-5p (-3p), miR-23a-5p, miR-24-3p, miR-29a-3p, miR-31, miR-101, miR-125b-1-3p, miR-126-3p, miR-146a-3p, miR-155-5p miR-195-5p, miR-206, miR-594 and let-7f-5p	miR-192-5p, miR-375-3p, miR-200b, miR-214-3p and miR-422b-5p	[14, 102, 108, 212, 261–263]

Table 2 Differentially expressed miRNA across various sample types in CD [159, 257]

Sample type	Upregulated miRNA	Downregulated miRNA	References
Peripheral blood	miR-16, miR-23a, miR-29a, miR-106a, miR-107, miR-126, miR-101, miR-146-5p, miR-146b-5p, miR-191, miR-199a-5p, miR-200c, miR-340, miR-362-3p, miR-375, miR-532-3p, miR-598, miR-642, and miRplus-E1271	miR-21, miR-31, miR-146a, miR-149, and miRplus-F1065	[106, 108, 162, 258–260, 264]
Feces	miR-15a-5p, miR-16-5p, miR-24-3p, miR-27a-3p, miR-126-3p, miR-128-3p, miR-142-5p, miR-155, miR-223-3p, miR-223-5p, and miR-3074-5p	miR-10a-5p, miR-10b-5p, miR-141-3p, miR-192-5p, miR-200a-3p, miR-375, miR-378-3p, and let-7g-5p	[106, 121, 166]
Saliva	miR-21, miR-31, and miR-142-3p	miR-26a, miR-101	[108]
Intestinal biopsy	miR-16, miR-19a, miR-21-3p, miR-23b, miR-30c, miR-31-3p, miR-101, miR-106a, miR-130a, miR-146a-3p, miR-155-5p, miR-191, miR-195, miR-223, and miR-594	miR-19b, miR-141, miR-200a, miR-200b, miR-200c, miR-375, miR-429, and miR-629	[98, 105, 108, 212, 261, 264, 265]

liposomes) and polymeric carriers (like cationic carriers). Ye et al. [233] discovered that administering lipofectamine-coated antisense miR-122a to colitis mice might reduce the inflammatory response. Tian et al. [79] discovered that peptosome-miR31 surrogates coated with oxidized konjac glucomannan demonstrated greater stability in comparison to polysaccharide- and liposome-based nanoparticles (NPs). Deng et al. [239] showed that intestinal macrophages are specifically targeted for mucosal regeneration in UC and colitis-associated cancer in DDS mice model by loading miR-146b mimic on mannose-modified trimethyl chitosan [MTC]-conjugated NPs. Exosomes have received the most attention in recent debate among these miRNAs. Exosomes are now commonly recognized as a natural NP carrier for targeted drug delivery, and miRNA mimics or inhibitors loaded into exosomes might be an efficient therapy for IBD [240, 241]. Cao et al. [207] discovered that enterotoxigenic *Bacteroides fragilis* might lower the amount of exosome-packed miR-149-3p in IBD patients' plasma. Notably, drug delivery via exosomes is still challenging due to several factors, including inadequate clinical-grade manufacturing, unstandardized separation and purification techniques, and low drug-loading efficiency [242]. The complex ecosystem in the GI tract of IBD patients may also restrict the efficacy of exosome-packaged miRNA mimics or inhibitors as treatments [159]. For these obstacles, we will need to produce cell-derived artificial exosomes or novel biomaterials in the near future to encapsulate miRNA mimics or inhibitors.

When comparing loss-of-function with gain-of-function approaches, replacing defective miRNA appears to be more difficult than producing anti-miRNA. Firstly, synthetic miRNA mimics must be integrated into the RISC complex to restore its biological function. Furthermore, the carrier must selectively target interested cells with sufficient quantity and efficacy to perform its action before clearance. Lastly, the most often utilized carrier is a viral vector, which is administered intravenously or colonically, through enema, and is strongly linked to toxicity and immunogenicity [243].

Clinical trials evaluating miRNA-associated drugs

ABX464 for UC

ABX464, also known as obefazimod, is a small molecule that specifically increases the expression of miR-124 in immune cells. ABX464 is an oral medication that was originally developed as an inhibitor of HIV replication and enhances the production of miR-124 from the miR-124.1 chromosomal region [244, 245]. ABX464 has been demonstrated to interact with the cap-binding complex, resulting in increased expression of miR-124. Preclinical research revealed that ABX464 offered long-term protection, alleviated DSS-induced colitis in mice, and triggered

the expression of IL-22, a cytokine implicated in colitis tissue healing. [246]. ABX464 was evaluated in phase 2a and 2b trials and was demonstrated to significantly ameliorate moderate-to-severe aUC when compared to placebo [247, 248]. A long-term maintenance phase was available to UC patients who finished the induction phase. For more details about the registration of the induction phase trial [249], long-term phase trial [250], and phase 2b clinical trial [251].

ABX464 for CD

Additionally, Abivax Company has started a phase 2a clinical trial to evaluate the efficacy and safety of ABX464 in moderate-to-severe aCD patients who have not responded well to previous treatments with amino-salicylic acid, corticosteroids, immunosuppressants, and/or biologics or who have become intolerant to them [252].

In future research, additional clinical trials should be extrapolated for IBD management, especially after demonstrating a promising effect against other disease conditions. For example; MRX34, a liposomal miR-34a mimic, in patients with advanced solid tumors [253], and Miravirsen, miR-122 antagomir, in patients with brain tumors [254] and hepatitis C virus (HCV) infection [255, 256].

Conclusion and future perspectives

IBD is a complex and multifactorial disease. The exact etiology of IBD is still out of reach, but it is associated with genetic and environmental factors. One of the main theories for the development of IBD is the dysbiosis of the intestinal ecosystem and the disruption of the intestinal barrier. Many miRNAs are involved in the complex pathways that regulate gut microbiome, intestinal integrity, and intestinal inflammation. Moreover, it appears that there are an infinite number of molecular interactions; currently, new research indicates that some miRNAs may be targeted as therapeutic targets or diagnostic biomarkers. Mimicking or inhibiting miRNA activity may represent a promising addition to the IBD therapeutic arsenal, as they have been demonstrated to be implicated in numerous IBD pathogenic pathways. On the other hand, human studies are scarce, and they generally focus on miRNA expression in certain cells and circumstances, leaving little information regarding their dynamic changes during inflammation and in response to treatments. Future in vivo research is required to confirm results from in vitro studies and investigate the efficacy of modifying miRNA expression in IBD.

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Declarations

Conflict of interest The authors declared no competing interests to be disclosed.

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