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# Implication of miRNAs for inflammatory bowel disease treatment: Systematic review

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## Abstract

Inflammatory bowel disease (IBD) is believed to develop *via* a complex interaction between genetic, environmental factors and the mucosal immune system. Crohn's disease and ulcerative colitis are two major clinical forms of IBD. MicroRNAs (miRNAs) are a class of small, endogenous, noncoding RNA molecules, and evolutionary conserved in animals and plants. It controls protein production at the post-transcriptional level by targeting mRNAs for translational repression or degradation. MiRNAs are important in many biological processes, such as signal transduction, cellular proliferation, differentiation and apoptosis. Considerable attention has been paid on the key role of miRNAs in autoimmune and inflammatory disease, especially IBD. Recent studies have identified altered miRNA profiles in ulcerative colitis, Crohn's disease and inflammatory bowel disease-associated colorectal cancer. In addition, emerging data have implicated that special miRNAs which suppress functional targets play a critical role in regulating key pathogenic mechanism in IBD. MiRNAs were found involving in regulation of nuclear transcription factor kappa B pathway (*e.g.*, miR-146a, miR-146b, miR-122, miR-132, miR-126), intestinal epithelial barrier function (*e.g.*, miR-21, miR-150, miR-200b) and the autophagic activity (*e.g.*, miR-30c, miR-130a, miR-106b, miR-93, miR-196). This review aims at discussing recent advances in our understanding of miRNAs in IBD pathogenesis, their role as disease biomarkers, and perspective for future investigation and clinical application.



**Key words:** Crohn's disease; Inflammatory bowel disease; MicroRNA; Treatment; Ulcerative colitis; Biomarker

**Core tip:** MicroRNAs (miRNAs) are a class of small, noncoding RNA molecules that post-transcriptionally regulate gene and protein expression. Recent studies have identified altered miRNA profiles in inflammatory bowel disease (IBD). Special miRNAs which suppress functional targets have been found to play a critical role in regulating key pathogenic mechanism in IBD. In this review, we discuss the possibility to use miRNAs as biomarkers and therapeutic target in IBD.

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## INTRODUCTION

Inflammatory bowel disease (IBD) refers to chronic remittent or progressive inflammatory conditions that may affect the entire gastrointestinal tract. Crohn's disease (CD) and ulcerative colitis (UC) are two major clinical forms of IBD[1]. The incidence and prevalence of IBD is continuously increasing over the past decades in different regions around the world[2]. Although the precise pathogenesis of IBD remains obscure, several reports have

indicated that dysfunction of the mucosal immune system which develops *via* a complex interaction between genetic factors, the host immune system and environmental factors plays an important role in its etiology[3]. The chronic inflammation of IBD is associated with marked molecular changes in gene and protein expression[4]. So small molecules targeted at the pathways involving in these processes may be potential for IBD diagnosis and treatment.

MicroRNAs (miRNAs) are considered as promising candidate. They are a class of single-stranded non-coding RNA molecules on an average 22 nucleotides long[5], and are highly conserved throughout evolution[6] and discovered in all eukaryotic cells except fungi[7]. MiRNAs regulate gene expression both at a transcriptional and translational level[8], and mediate post-transcriptional gene silencing by directly binding to the 3' untranslated region (UTR) of target mRNA. Depending on the level of sequence complementarity between miRNA and target site, mRNA transcripts targeted by miRNAs are either silenced if the base-pair match is imperfect or degraded if there is an identical base-pair match[9]. The mRNAs inhibited by miRNAs move to cytoplasm and accumulate in cytosolic processing bodies until they are eventually degraded[10]. Each miRNA can target hundreds of genes, and a particular gene is usually the target of multiple miRNAs, adding complexity to the regulation of gene transcriptional network[11]. It has been reported that miRNAs play an important role in many biological processes, such as signal transduction, cellular proliferation, differentiation, apoptosis and immune response[12,13]. Recently, miRNAs have been recognized as critical elements in the regulation of the innate and adaptive immune responses, and changes in miRNAs expression are related to many autoimmune diseases, including systemic lupus erythematosus, rheumatoid arthritis, psoriasis and IBD[14-17].

In this review, we summarize the current understanding of the connection between miRNAs and IBD. We mainly focus on special dysregulated miRNAs in CD and UC, which lead to inappropriate expression of targeted mRNA and may contribute to IBD pathogenesis, diagnosis and treatment. Table 1 summarizes the altered miRNAs involved in IBD and their mRNA targets.

## MIRNAS REGULATE NUCLEAR TRANSCRIPTION FACTOR KAPPAB PATHWAY

The nuclear transcription factor kappaB (NF-κB) was identified as one of the important regulators in the immune system and inflammatory diseases[18]. NF-κB is markedly induced in IBD patients and strongly influences the course of mucosal inflammation through its ability to promote the expression of various pro-inflammatory genes[19]. Nucleotide-binding oligomerization domain 2 (NOD2) was found to be the first IBD susceptibility gene[20], which is mainly expressed in Paneth cells, monocytes, macrophages, dendritic cells and some types of intestinal epithelia cell[21]. NOD2 can be activated by muramyl dipeptide (MDP), a component of bacterial cell wall, which induces the activation of NF-κB[22].

MiR-146a was reported to regulate gut inflammation *via* NOD2-sonic hedgehog (SHH) signaling[23]. SHH signaling is an important pathway that maintains gut homeostasis and directs gut development. The expressions of NOD2-induced iNOS and NO were increased in MDP-treated macrophages, which further induced the level of miR-146. Promoter luciferase analysis with miR-146a promoters revealed that NF-κB was a critical transcription factor that regulate NOD2 mediated expression of miR-146a. NOD-2 induced miR-146a target NUMB, a negative regulator of SHH signaling, alleviating the suppression of SHH signaling and subsequently increasing the pro-inflammatory cytokines expression.

Feng *et al*[24] proved that up-regulation of miR-126 may contribute to pathogenesis of UC by targeting IκBα. They found miR-126 was significantly increased in active UC tissues compared to healthy controls. IκBα, an inhibitor of NF-κB pathway and the target of miR-126, was markedly decreased in active UC tissues. The expression of miR-126 and IκBα were inversely correlated in patients with active UC. MiR-126 could inhibit the level of IκBα in HT29 cells. They further demonstrated that miR-126 may activate NF-κB signaling pathway by targeting IκBα and contribute to the development of UC. Another study showed that the anti-inflammatory activities of the red wine polyphenolics were, at least in part, mediated by the induction of miR-126[25]. CAMs, such as intracellular cell adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1), are expressed on the surface of fibroblasts[26]. It has been demonstrated that the expression of ICAM-1 was increased in CD patients[27] and inhibition of CAMs could suppress various forms of experimental inflammatory and immune responses in colon fibroblast cells[28]. VCAM-1 has been confirmed as one of the targets of miR-126 before[29]. Angel-Morales *et al*[25] found the polyphenolic red wine extract (WE) exerted an anti-inflammatory effect in LPS-stimulated human colon-derived CCD-18Co myofibroblast cells through inactivating NF-κB and down-regulating a wide range of downstream pro-inflammatory genes including tumor necrosis factor (TNF)-α, interleukin-6 (IL-6) and CAMs. Furthermore, they found the up-regulation of miR-126 was induced by WE in CCD-18Co cells and protected human colon cells from inflammation through targeting VCAM-1.

MiR-122 was found dysregulated in association with CD progression[30]. Chen *et al*[31] identified NOD2 as a target of miR-122. Overexpression of miR-122 in LPS-stimulated HT-29 cells inhibited LPS-induced apoptosis and down-regulated LPS-induced NOD2 expression. Pretreatment with miR-122 in LPS-stimulated HT-29 cells decreased the pro-inflammatory cytokines and increased the anti-inflammatory cytokines by targeting NOD2-induced NF-κB signaling pathway. Taken together, miR-122 might decrease intestinal epithelial cell injury in Crohn's disease by targeting NOD2. Besides regulating the activation of NF-κB pathway, Ye *et al*[32] demonstrated

**Table 1 List a core set of altered microRNAs involved in inflammatory bowel disease and their mRNA targets**

| miRNA | Target mRNA | Net effect | Ref. |
|---|---|---|---|
| Increased expression | | | |
| miR-146a | NUMB | SHH signaling upregulation | [23] |
| miR-146b | Siah2 | NFκB signaling upregulation | [40] |
| miR-126 | IκBα | NFκB signaling upregulation | [24] |
| | Vascular cell adhesion molecule-1 | Suppresses proinflammatory cytokines | [25] |
| miR-122 | Nucleotide-binding oligomerization domain 2 | Decreases intestinal epithelial cell injury | [31] |
| | Occluding | Intestinal permeability upregulation | [32] |
| miR-132 | AChE | Decreases circulation AChE activity | [37] |
| miR-21 | RhoB | Impairment of tight junctions | [52,53] |
| miR-150 | c-Myb | Promotes apoptosis | [54] |
| miR-141 | CXCL12β | Regulates leukocyte migration | [62] |
| miR-106b | ATG16L1 | deregulation of autophagy | [67,68] |
| miR-196 | IRGM | deregulation of autophagy | [70] |
| miR-30c | ATG5 | inhibition of autophagic activity | [69] |
| miR-130a | ATG16L1 | inhibition of autophagic activity | [69] |
| Decreased expression | | | |
| miR-10a | IL-12/IL-23p40 | Regulates intestinal homeostasis | [43] |
| miR-124 | STAT3 | Promotes inflammation | [48] |
| miR-200b | ZEB1, SMAD2 | Regulates epithelial-mesenchymal transition | [59,60] |
| miR-192,miR-495, miR-512,miR-671 | NOD2 | NFκB signaling upregulation | [34] |

NF-κB: Nuclear transcription factor kappa B; NOD2: Nucleotide-binding oligomerization domain 2; AChE: Acetylcholinesterase; IRGM: Immunity-related GTPase family; IL: Interleukin; ZEB1: Zinc finger E-box binding homeobox 1; SMAD2: SMAD family member 2.

the involvement of miR-122 in the regulation of intestinal epithelial tight junction (TJ) permeability. Deficient intestinal epithelial TJ barrier, characterized by the increase of intestinal permeability, has been demonstrated to contribute to the development of IBD as an important pathogenic factor[33]. MiR-122 was significantly increased in TNF-α-stimulated Caco-2 cells and induced the increase in Caco-2 TJ permeability by targeting occluding. The up-regulation of intestinal permeability by miR-122 was proved *in vivo* as well[32]. Based on the two studies, miR-122 plays a complex and controversial role in the development of IBD.

Chuang *et al*[34] showed that NOD2 expression is regulated by miRNAs in HCT116 cells. They found that MDP could induce the expression of NOD2 and activate the NF-κB signaling pathway in HCT116 cells. MiRNAs targeted NOD2, such as miR-192, miR-495, miR-512 and miR-671, were significantly decreased in MDP-stimulated HCT116 cells, which had an inversely correlation with the expression of NOD2. Overexpression of these NOD2-associated miRNAs in MDP-stimulated HCT116 cells inhibited the activity of NF-κB and the downstream pro-inflammatory cytokines, IL-8 and CXCL3.

MiR-132 was a potential regulator of acetylcholinesterase (AChE) activity in inflammatory condition and was shown to target AChE to reduce its activity *in vitro* and in mouse models[35]. Acetylcholine (ACh) activates its receptor on macrophage through which it interrupts the nuclear translocation of NFκB and suppresses the production of pro-inflammatory cytokines[36]. Maharshak *et al*[37] found miR-132 had an anti-inflammatory effect on the development of IBD. MiR-132 level was significantly upregulated in biopsies from patients with IBD compared with controls. In accordance with this, circulation AChE activity was significantly lower in patients with IBD suffering from moderate-severe disease. These data implicated a possible regulation of AChE activity by increased miR-132 levels, which eventually ameliorated inflammation in patients with IBD.

Although NFκB was originally thought to be an almost exclusively pro-inflammatory player in the setting of IBD, its role in epithelial cells was confirmed more controversial. Several studies using knockout mice with defective NF-κB activation have demonstrated an anti-inflammatory function of NFκB in colonic epithelial cells[38,39]. Nata *et al*[40] showed that miR-146b, another member of miR-146 family, can alleviate intestinal injury in mouse colitis *via* the activation of NF-κB and the improvement of epithelial barrier function. MiR-146b was found significantly up-regulated in IL-10 deficient mice. The whole sequence of miR-146 was intraperitoneally administered to the dextran sodium sulfate (DSS)-induced colitis mouse. Overexpression of miR-146b in DSS-induced colitis mouse activated NFκB, relieved intestinal inflammation, improved epithelial barrier function, and increased the survival rate. Furthermore, the protective effect of miR-146b on mouse with DSS-induced colitis was negated by inhibition of the NFκB pathway. Siah2, which was the target of miR-146b, promoted ubiquitination of TRAF proteins upstream of NFκB. It suggested that miR-146b up-regulated NFκB *via* suppressing siah2, which finally improved intestinal inflammation.

## MIRNAS REGULATE IL-23/IL-23R PATHWAY

IL-23, a heterodimeric cytokine comprising IL-12p40

and IL-23p19, is produced by activated macrophages, monocytes, DCs and endothelial cells. IL-23 receptor is composed of IL-12Rβ1 (shared with the IL-12 receptor) and the specific IL-23R subunit. IL-23 acts on the IL-23 receptor and promotes expansion and maintenance of Th17 cells, which secrete the pro-inflammatory cytokine IL-17 and have been implicated in the pathogenesis of many chronic inflammatory disorders, including IBD[41,42]. MiRNA was considered as a new mechanism in regulating the IL-23/TH17 pathway and subsequent downstream IL-17 production in IBD.

Xue *et al*[43] found much lower expression of miR-10a in intestinal epithelial cells and dendritic cells of specific pathogen-free mice compared to germ-free mice. IL-12/IL-23p40 was identified as a target of miR-10a. They further demonstrated that microbiota negatively regulated host miR-10a expression by targeting IL-12/IL-23p40, which may contribute to the maintenance of intestinal homeostasis.

*IL-23R* gene variants have been identified as risk factors for IBD[44]. The rs10889677 variant in the 3'UTR region of *IL-23R* gene which led to a loss of binging capacity for let-7e and let-7f displayed increased expression of IL-23R[45]. It means this mutation sustained IL-23 signaling and contributed to chronicity of IBD. Furthermore, Li *et al*[46] showed let-7f down-regulated the expression of IL-23R and its downstream cytokine IL-17 by targeting IL-23R.

## MIRNAS REGULATE IL-6/STAT3 PATHWAY

Previous studies have shown the importance of the IL-6/STAT3 signaling pathway in IBD. Inhibition of IL-6/STAT3 cascades results in the suppression of acquired immune mediated colitis[47]. Koukos *et al*[48] found miR-124 were significantly decreased in colon tissues from children with UC and mice with experimental colitis, and the levels of STAT3 and its regulated genes were up-regulated simultaneously. They demonstrated reduced levels of miR-124 in colon tissues of pediatric patients with active UC might increase expression and activity of STAT3 by direct binding to its 3'UTR, which could promote inflammation and the pathogenesis of UC in children.

## MIRNAS REGULATE INTESTINAL EPITHELIAL BARRIER FUNCTION

The intestinal mucosal barrier, of which the intestinal epithelial cells are the most integral part, maintains a delicate balance between absorbing essential nutrients while preventing the entry and responding to harmful subjects[49]. Dysfunction of intestinal epithelial barrier has been extensively reported in IBD[49,50].

Disruptions of important elements of the intestinal barrier in IBD lead to permeability defects[51]. There were two studies showed that miR-21 played a pro-inflammatory role in IBD by impairing intestinal barrier function. Yang *et al*[52] found levels of miR-21 were up-regulated in both the mucosal and serum of patients with UC. RhoB, which was the target of miR-21 and involved in modulating intestinal epithelial permeability, was found significantly decreased in the patients with UC. They demonstrated that overexpression of miR-21 in patients with UC and Caco-2 cells impaired intestinal tight junction integrity and morphology through targeting RhoB. Similarly, Shi *et al*[53] reported that miR-21 was overexpressed in IBD patients, IL-10 KO mice and DSS-treated mice. MiR-21 knockout (KO) mice was less susceptible to experimental colitis and had more ameliorative inflammatory responses than wild type (WT) mice. Moreover, the increase of Intestinal permeability and epithelial cells apoptosis induced by DSS were attenuated in miR-21 KO mice.

Bian *et al*[54] found miR-150 was significantly elevated, whereas c-Myb, a target of miR-150, was strongly decreased in colon tissue of UC patients and DSS-treated mice. Overexpression of miR-150 in HT29 cells enhanced cell apoptosis through targeting c-Myb, which damaged intestinal epithelial barrier.

Epithelial-to-mesenchymal-transition (EMT) is characterized by losing epithelial cell markers such as E-cadherin and gaining mesenchymal proteins including vimentin, which enhances invasiveness, migratory capacity and production of cell-extracellular matrix components[55,56]. Recent studies demonstrated that EMT contributed to the loss of intestinal epithelial cells (IECs) and subsequent increased intestinal paracellular permeability and decreased intestinal epithelial barrier function[57,58]. Chen *et al*[59] found miR-200b significantly decreased in inflamed mucosa in IBD patients, which was positively correlated to the expression of E-cadherin and negatively correlated to the level of TGF-β1 and vimentin. Overexpression of miR-200b in TGF-β1-stimulated IEC-6 cells increased E-cadherin and decreased vimentin through targeting zinc finger E-box binding homeobox 1 and SMAD2 respectively, which prevented TGF-β1-induced EMT. Intestinal fibrosis is a common serious complication of CD. In another study, they demonstrated that miR-200b could partially protect intestinal epithelial cells from fibrogenesis by suppressing EMT *in vitro*[60]. In summary, miR-200b played a potential role in maintaining intact of intestinal epithelium through inhibiting EMT and improving pathophysiology and clinical outcomes of IBD.

## MIRNAS REGULATE COLONIC EPITHELIAL CELL-DERIVED CHEMOKINE EXPRESSION

The expression of intestinal epithelial-derived CXC and CC chemokines is increased in IBD[61]. Huang *et al*[62] found up-regulated level of miR-141 was inversely correlated with CXCL12β in the epithelial cells of the inflamed colon tissues from CD patients and mice with experimental colitis.They further demonstrated that miR-141 directly regulated CXCL12β expression and leukocyte migration

mediated by CXCL12β. Additionally, overexpression or knockdown of miR-141 in the colon of mice with experimental colitis regulated leukocyte infiltration and alleviated or aggravated intestinal inflammation, respectively. Wu *et al*[63] found miR-192 was decreased in active UC and demonstrated an inverse relationship between miR-192 and MIP-2 (CXCL2).

## MIRNAS REGULATE AUTOPHAGY

Autophagy, which is involved in recycling cellular organelles for the survival of cell, is one mechanism for maintaining cellular hemostasis. Autophagy in the intestinal epithelium is considered to behave as a defensive strategy for clearance of intracellular microorganisms, and the impairment of autophagy results in intestinal epithelial dysfunction and contributes to IBD pathogenesis[64]. *ATG16L1* and *IRGM*, two genes associated with autophagy, have been identified as CD susceptibility genes by genome-wide association studies[65,66]. Some studies showed that miRNA-mediated change in the expression of autophagy gene may result in autophagy dysfunction and involve in the pathogenesis of IBD.

Lu *et al*[67] found that silencing of Dicer1 enhanced autophagy-related gene (ATG) protein levels and autophagosome formation in cells, indicating that miRNAs may be implicated in the regulation of autophagy. MiR-106b and miR-93, which target ATG16L1, both reduced levels of autophagy in epithelial cells. MiR-106b could also inhibit autophagy-dependent clearance of CD-associated adherent-invasive Escherichia col (AIEC) in epithelial cells. Inflamed mucosae from subjects with active CD exhibited more overexpressed miR-106b and lower expression of ATG16L1 when compared with controls. These results suggested that CD patients with miR-106b and miR-93 mediated down-regulation of ATG16L1 expression might manifest an altered antibacterial activity of CD-associated intracellular bacteria in epithelial cells and subsequently affected the outcome of intestinal inflammation. Similarly, Zhai *et al*[68] showed miR-106b targeted ATG16L1 and modulated autophagic activity in HCT116 cells. Their results further indicated that miR-106a and miR-106b could influence the expression of other autophagy-related genes and had a widespread modulating effect on the autophagy pathway.

Nguyen *et al*[69] proved miR-30c and miR-130a directly regulated the expression of ATG5 and ATG16L1, respectively, by targeting their 3'UTRs. They found miR-30c and miR-130a expression were increased and ATG5 and ATG16L1 mRNA expression were decreased in non-inflamed or inflamed ileal CD biopsy specimens compared with normal controls. Similarly, the expression of miR-30c and miR-130a were inversely correlated with ATG5 and ATG16L1 in intestinal epithelial T84 cells infected with the AIEC. NF-κB pathway was activated in AIEC infected T84 cells, which induced the up-regulation of miR-30c and miR-130a and consequently inhibited the expression of ATG5 and ATG16L1. The inhibition of autophagic activity by miR-30c and miR-130a increased AIEC persistence within T84 cells and enhanced pro-inflammatory cytokines production. Furthermore, they demonstrated inhibition of miR-30c and miR-130a *in vivo* suppressed AIEC-induced down-regulation of ATG5 and ATG16L1 expression and increased autophagic activity, leading to more efficient intracellular bacteria clearance and decreased inflammation.

Brest *et al*[70] demonstrated that the association of IRGM with CD arised from a miRNA-based alteration in IRGM regulation which led to the deregulation of autophagic efficacy. They found a synonymous variant in IRGM (c.313C > T), which was classified as non-causative before, altered a binging site for miR-196. MiR-196, was overexpressed in the inflammatory intestinal epithelia of patients with CD and down-regulated the IRGM protective variant (c.313C) but not the risk-associated allele (c.313T). Subsequent deregulation of IRGM-dependent autophagy compromised control of intracellular replication of CD-associated AIEC and affected the outcome of intestinal inflammation.

## MIRNAS ASSOCIATION WITH IBD CARCINOGENESIS

The development of IBD-associated dysplasia and colorectal cancer represents a major complication in patients with IBD[71,72]. The important role miRNAs played in carcinogenesis is becoming clearer because miRNAs have been referred to the regulation of cancer-related cellular processes, including differentiation, apoptosis, cell cycle progression and immune function[10]. Growing evidence implicated that miRNAs are also involved in IBD-associated carcinogenesis.

Ludwig *et al*[73] showed up-regulated level of miR-21 in IBD-associated dysplastic lesions compared to active IBD patients, which was inversely correlated with the expression of PDCD4, a newly characterized tumor suppressor gene. Olaru *et al*[74,75] found expressions of miR-224 and miR-31 increased successively at each stage of IBD progression from non-inflamed to inflamed non-neoplastic, dysplastic and finally cancerous mucosae. MiR-224 and miR-31 levels could accurately discriminate normal or chronically inflamed IBD tissues from cancers. They further identified miR-224 regulated cell cycle through targeting p21 and miR-31 regulated tumor angiogenesis by targeting factor inhibiting hypoxia inducible factor 1, both of which subsequently participated in IBD-associated carcinogenesis.

## FUTURE PERSPECTIVE IN IBD DIAGNOSTIC AND TREATMENT

Investigations described above showed that special miRNAs suppressing functional targets played a pro-inflammatory or anti-inflammatory role in regulating the pathogenic mechanism of IBD, including activation of NFκB, increased intestinal epithelial permeability, abnormal autophagic activity and so on. It means inflam-

matory response, intestinal epithelial barrier and other mechanisms involved in IBD can be regulated by targeting miRNAs, indicating the potential of miRNAs as therapeutic targets for IBD. Besides studying the function of IBD-associated miRNAs *in vitro*, some researchers had administrated miRNAs into mice with experimental colitis by different methods to investigate their functional and therapeutic effect *in vivo*. Inhibition of miR-30c and miR-130a in mice by ileal loop assay suppressed AIEC-induced down-regulation of ATG5 and ATG16L1 expression and decreased intestinal inflammation[69]. Overexpression of miR-146b in DSS-induced colitis mouse *via* intraperitoneal injection relieved intestinal inflammation and increased the survival rate of mouse[40]. MiR-141 intracolonic administration in the colon of TNBS-induced and IL-10 KO mice regulated leukocyte infiltration and alleviated intestinal inflammation[62]. These data showed the effective ways to administrate miRNAs into human and the possibilities for the future clinical applications of miRNA-based therapeutic approaches in IBD.

There have been several studies that identified altered miRNA profiles in both serum and inflamed tissue in patients with UC and CD compared with controls, which have been reviewed by Coskun *et al*[76]. Circulating miRNAs in serum exist in membrane vesicles, such as exosomes[77], or form a complex with lipid protein carriers, such as high-density lipoproteins (HDL)[78]. So these circulating miRNAs are protected from blood RNAses and relatively stable compared with mRNA and protein, which make themselves serving as ideal noninvasive blood biomarkers in patients with IBD. In addition, the aberrant expression of miRNAs in inflamed tissues of patients with UC could also help in IBD diagnosis.

## CONCLUSION

MiRNAs are a class of potential gene regulators of critical importance in the pathogenesis of IBD. It has been demonstrated that miRNAs have the possibility to be used as biomarkers and therapeutic target in IBD. Although our knowledge about the miRNAs regulation of IBD has considerably advanced over the last several years, multiple areas warrant future investigation. Most studies have focused on one miRNA which targets a single mRNA. One area worth future investigation is a key miRNA targeting multiple mRNAs or several miRNAs combination targeting a key mRNA. The other area worth future investigation focuses on the roles of miRNAs in human studies. Most of our understanding of the functions of miRNAs associated with IBD is based on cell cultures and murine models. Further investigating the roles of miRNAs in the human context will improve our knowledge of miRNAs in the pathogenesis and diagnosis of IBD and pave the way for miRNA-based therapies.

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