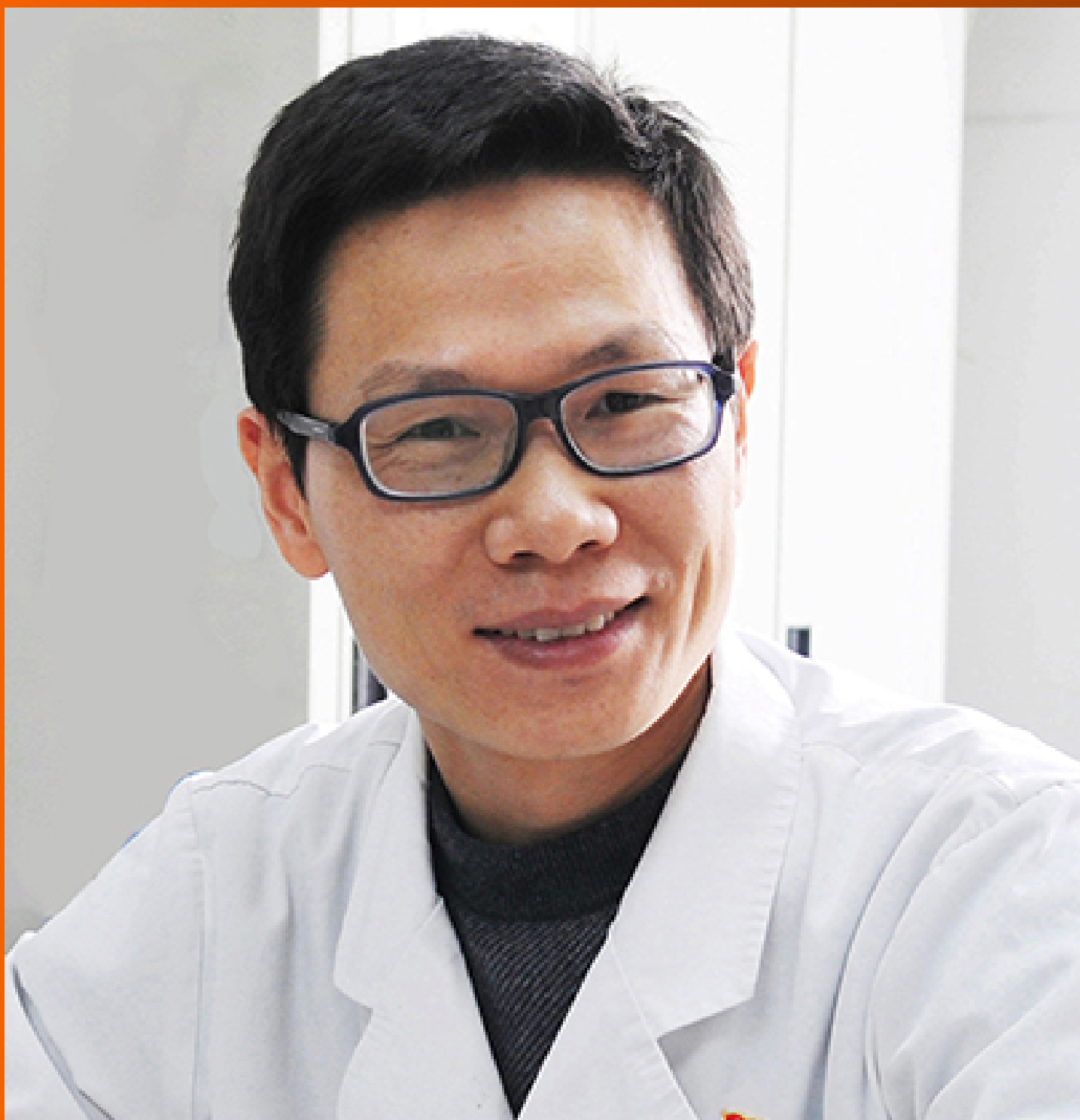


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MicroRNAs in inflammatory bowel disease: What do we know and what can we expect?

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Abstract

MicroRNAs (miRNAs), small non-coding RNAs composed of 18–24 nucleotides, are potent regulators of gene expression, contributing to the regulation of more than 30% of protein-coding genes. Considering that miRNAs are regulators of inflammatory pathways and the differentiation of intestinal epithelial cells, there is an interest in exploring their importance in inflammatory bowel disease (IBD). IBD is a chronic and multifactorial disease of the gastrointestinal tract; the main forms are Crohn's disease and ulcerative colitis. Several studies have investigated the dysregulated expression of miRNAs in IBD, demonstrating their important roles as regulators and potential biomarkers of this disease. This editorial presents what is known and what is expected regarding miRNAs in IBD. Although the important regulatory roles of miRNAs in IBD are clearly established, biomarkers for IBD that can be applied in clinical practice are lacking, emphasizing the importance of further studies. Discoveries regarding the influence of miRNAs on the inflammatory process and the exploration of their role in gene regulation are expected to provide a basis for the use of miRNAs not only as potent biomarkers in IBD but also as therapeutic targets for the control of inflammatory processes in personalized medicine.

Key Words: MicroRNAs; Inflammatory bowel disease; Crohn's disease; Ulcerative colitis; Biomarker; Therapy

Core Tip: MicroRNAs (miRNAs) function in the regulation of inflammatory pathways and the differentiation of intestinal epithelial cells. There is substantial evidence for the important regulatory roles of miRNAs in inflammatory bowel disease (IBD), suggesting that they may serve as biomarkers. Therefore, this editorial aims to present what is already known and what the expectations are regarding the role of miRNAs in IBD.

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INTRODUCTION

MicroRNAs (miRNAs) are small non-coding RNAs composed of 18 to 24 nucleotides that are recognized as potent downregulators of gene expression or messenger RNA translation[1-3]. They regulate more than 30% of protein-coding genes and play important roles in cell survival, differentiation, proliferation, apoptosis, cell cycle control, and homeostasis[1,2,4].

Because miRNAs regulate inflammatory cellular signaling pathways and the intestinal epithelial cell differentiation, with an important role in the homeostasis of the intestinal mucosa[1,5,6], we explored the importance of miRNAs in inflammatory bowel diseases (IBD). IBD is a chronic disease of the gastrointestinal tract with a multifactorial and imbricated etiology, involving genetic, immune, and environmental factors. The main representatives of IBD are Crohn's disease (CD) and ulcerative colitis (UC), which differ both clinically and pathophysiologically[7].

In the last decade, several clinical and experimental studies of IBD have improved our understanding of miRNAs and contributed to the search for new and more accurate diagnostic markers and targets for treatment. Based on this, this editorial aims to present what is already known and what the expectations are regarding the role of miRNAs in IBD.

WHAT DO WE KNOW ABOUT MIRNA IN IBD?

miRNAs play an important role as cellular and homeostasis regulators and may interfere with important inflammatory signaling pathways, such as the nuclear transcription factor kappa B (NF-κB), interleukin 23 (IL23)/IL23R, and IL-6/STAT3 pathways[8-11]. Therefore, alterations in the expression of certain miRNAs may be related to various immune diseases, including IBD. To evaluate their expression profiles in diseases, miRNAs can be quantified using samples of body fluids (circulating miRNAs), such as blood and feces, as well as through homogenized tissue biopsies (tissue miRNAs) using microarray profiling, quantitative real-time PCR, and next-generation sequencing techniques[12-15].

One of the first studies focusing on miRNAs in IBD identified three under expressed miRNAs (miR-192, miR-375, and miR-422b) and eight overexpressed miRNAs (miR-16, miR-21, miR-23a, miR-24, miR-29a, miR-126, miR-195, and Let-7f) in tissues from patients with active UC compared to tissues from healthy individuals[5]. Another study conducted by the same research group evaluated colonic tissues from patients with CD and identified three upregulated miRNAs (miR-23b, miR-106a, and miR-191) and two downregulated miRNAs (miR-19b and miR-629) when compared with levels in colonic tissues from healthy individuals[6]. Neither upregulated nor downregulated miRNAs in CD patients with were altered in UC patients[6], indicating that the miRNA expression profile differs between CD and UC.

These studies prompted researchers to investigate the role of miRNA dysregulation in IBD, both as regulators of inflammatory processes and as IBD biomarkers. Several studies have focused on the detection of miRNA biomarkers for IBD, revealing miR-223, miR-155, and miRNA-320a as key candidates.

A study using serum samples from IBD patients suggested that miR-223 is a potential biomarker, as levels of this miRNA were higher in both CD and UC samples than in healthy individuals[16]. Additionally, miR-223 expression is associated with the active phase of the disease[16]. Another study using the same sample type corroborated the increase in miR-223 expression in patients when compared with that in healthy individuals[17]. However, when active patients were compared with those in remission, miR-223 expression showed no significant differences[17]. Similarly, miR-155 expression differed between patients and healthy individuals[17], and this was corroborated by another study that demonstrated higher miR-155 expression levels in the colon tissues of patients than in samples from healthy individuals [18], suggesting that miR-155 is a potential biomarker of IBD activity. Similarly, a recent study on IBD demonstrated that miR-320a expression is higher in blood samples of IBD patients than in samples from healthy individuals and is significantly higher in patients with active IBD than in patients in remission[19], highlighting that miR-320a is another promising biomarker of disease activity in IBD patients.

The search for miRNA biomarkers of IBD has also led to the identification of the roles of miRNAs in inflammatory signaling pathways modulated by various drugs, such as prednisone, Janus kinase (JAK) inhibitors, and monoclonal antibodies, including infliximab, ustekinumab, and vedolizumab (Figure 1). Furthermore, some miRNAs can be regulated

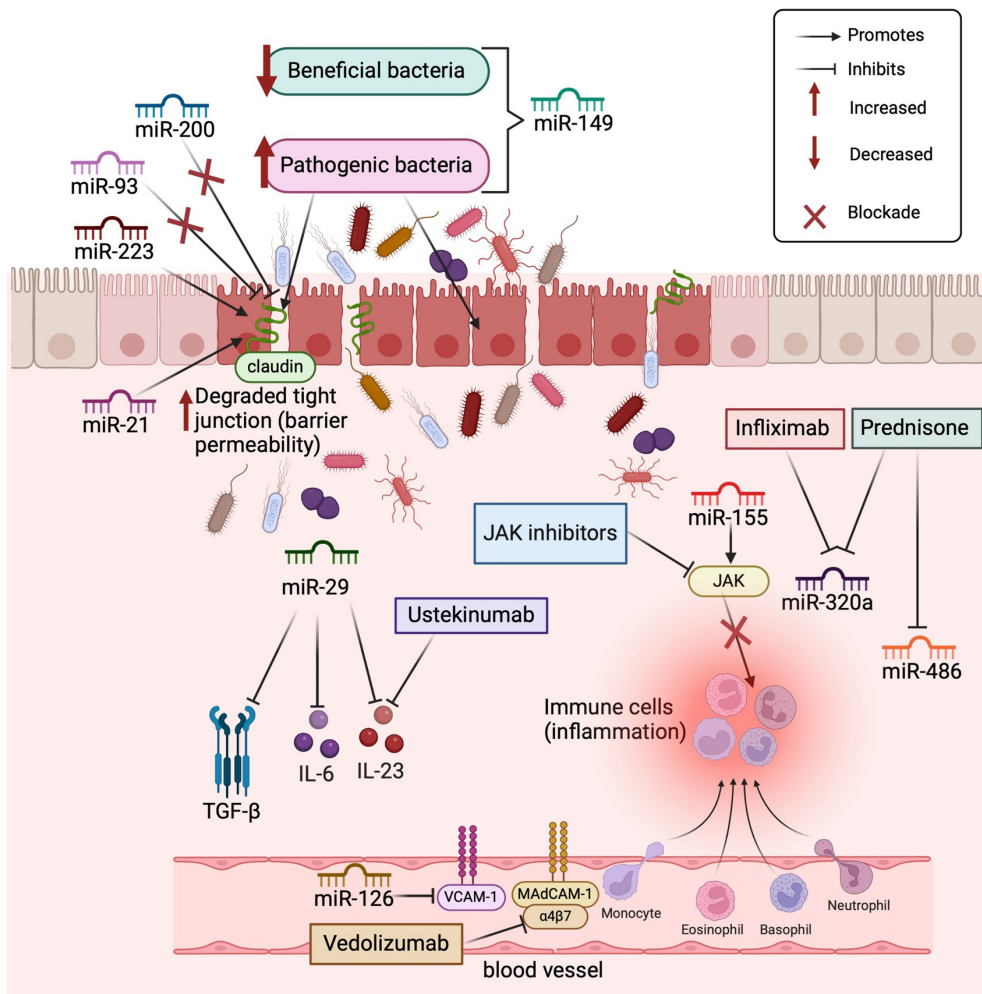


Figure 1 Main microRNAs involved in intestinal inflammation and inflammatory pathways targeted by medications used to treat inflammatory bowel disease. MicroRNA (miR)-21 and miR-223 inhibit tight junctions, whereas miR-200 and miR-93 maintain tight junctions. miR-149 promotes changes in the intestinal microbiota, favoring the growth of pathogenic bacteria. Prednisone reduces miR-486 expression, while miR320a expression is reduced by prednisone and infliximab. miR-29 reduces the expression of transforming growth factor β , interleukin (IL)-6, and IL-23, similar to ustekinumab, a biological inhibitor of IL12/23. miR-155 regulates the activity of Janus kinase (JAK), which activates immune cells, whereas JAK inhibitors exert the opposite effects. miR126 regulates vascular cell adhesion molecule-1 (VCAM-1), similar to vedolizumab, which regulates mucosal addressin cell adhesion molecule-1 (MAdCAM-1). $\alpha 4\beta 7$: A4 β 7 integrin. Created with BioRender.com (Supplementary material).

when exposed to certain drugs, as demonstrated in the pediatric population, where it was observed that miR-146a, miR-146b, and miR-320a were reduced with the use of infliximab and prednisone, whereas miR-486 expression was reduced only with the use of prednisone[20].

In a study of dextran sodium sulfate (DSS)-induced intestinal inflammation in mice, tail vein injection of miR-29 linked to a nanoparticle significantly inhibited the intestinal anti-inflammatory process, which was related to reductions in transforming growth factor- β , IL-6, and IL-23 expression[21]. Notably, the cytokine IL-23 is the target of the monoclonal antibody ustekinumab, which is currently used to treat CD, indicating that miR-29 is a potential therapeutic target for IBD. In contrast, miR-155 targets regulatory proteins in the JAK signaling pathway, which controls immune cells and, consequently, inflammatory processes[22]. This mechanism is the same as that of JAK inhibitors, such as tofacitinib and upadacitinib, which are oral drugs used to treat UC.

In vitro and *in vivo* analyses have shown that miR-126 inhibits leukocyte adhesion to endothelial cells through the regulation of vascular cell adhesion molecule-1 (VCAM-1)[23]. Vedolizumab, indicated for the treatment of UC and CD, also inhibits the migration of leukocytes into inflamed intestinal tissue, blocking their interaction with mucosal addressin-cell adhesion molecule 1 (MAdCAM-1) in the intestinal vasculature[24], a mechanism similar to that described for miR-126. The development of new drugs capable of modulating the expression of these miRNAs is a promising approach for controlling the inflammatory response.

Other studies have also reported an important relationship between miRNAs and intestinal permeability, considering that a loss of the intestinal barrier is one of the processes that triggers intestinal inflammation in IBD patients[25,26]. In this context, miR-21 plays an important role in regulating the intestinal epithelial barrier, as it blocks the production of the RhoB (Ras homolog gene family member B) protein[25]. A reduction in RhoB protein levels results in the loss of tight junctions, increasing intestinal permeability with subsequent increased exposure to antigens, which serves as a trigger for the intestinal inflammatory process[25].

Besides miR-21, other miRNAs destroy tight junctions and consequently weaken the intestinal epithelial barrier, including miR-191, miR-212, miR-675, miR-874, miR-122a, miR-34c, miR-150, and miR-01a[26]. In contrast, miR-200 and miR-93 assist in the protection of tight junctions, maintaining intestinal barrier function[26]. These recent findings indicate that several miRNAs are important targets for the development of treatments aimed at maintaining the integrity of the intestinal barrier, thereby preventing overexposure to antigens as a trigger in the inflammatory processes involved in IBD pathophysiology.

A recent review published by our research group[27] reported that some miRNAs modulate the intestinal microbiota and induce dysbiosis in IBD patients, whereas the intestinal microbiota can also regulate the expression of miRNAs, establishing a complex relationship between these taxa and their host[27]. For example, in a DSS-induced intestinal inflammation model, miR-149 deletion induces changes in the microbiota and promotes intestinal inflammatory processes [28]. Additionally, the use of probiotics in mice, in addition to improving dysbiosis, reduces the expression of miR-155, miR-223, miR-150, and miR-143, which act on both intestinal permeability and the pro-inflammatory response, improving intestinal inflammation[29].

WHAT CAN WE EXPECT FROM MIRNAS IN IBD?

From the first studies on miRNAs to recent research, there has been a great evolution in our understanding of their functions in the immune system and inflammatory processes. Despite this, there is a lack of data to support the use of miRNAs as biomarkers for chronic diseases, such as IBD, limiting the application of scientific knowledge to clinical practice. To date, specific miRNAs have not been described as biomarkers for differentiating UC from CD, as markers of inflammatory activity, or as predictors of response to clinical treatment. However, research work has yielded new discoveries and insights into the roles of miRNAs in the pathogenesis and maintenance of the inflammatory process in IBD. In the near future, these findings are expected to lead to novel applications of these biomarkers in clinical practice.

Regarding IBD monitoring, few biomarkers for disease activity, such as fecal calprotectin, have been validated[30,31] and therefore colonoscopy is needed to visualize the intestinal mucosa. Considering that colonoscopy is invasive with inherent risks, new markers with high accuracy are required. miRNAs participate in various processes, including inflammation. Therefore, miRNAs can serve as appropriate biomarkers for the diagnosis and therapeutic monitoring of IBD patients. In addition to contributing to a more specific diagnosis and treatment, the identification of miRNAs as blood or fecal markers of IBD provides a less invasive[8], faster, and more accurate alternative to colonoscopy. The disadvantage of miRNA markers is the high cost of tests, which hinders their applicability in clinical practice.

Regarding the role of miRNAs in differentiating disease activity from remission, miR-223 expression is higher in the serum, tissue from the terminal ileum, and fecal samples of active CD compared to inactive CD[32]. Furthermore, miR-223 levels in serum, intestinal tissue, and fecal samples were correlated with Crohn's Disease Activity Index, and fecal miR-223 was correlated with fecal calprotectin. These findings indicated that fecal miR-223 may be a novel, noninvasive biomarker for estimating disease activity in CD patients[32].

The Selecting Therapeutic Targets in IBD (Stride) II and IBD consensus established clinical response and remission as well as normalization of C-reactive protein as immediate and short-term targets, and endoscopic healing, restoration of quality of life, and absence of disability as long-term targets in IBD treatment, including mucosal healing as therapeutic goals[33,34]. The expectations include histological healing in UC and transmural healing in CD[33]. The identification of specific miRNAs correlated with mucosal healing, histological healing, or even transmural healing would be a revolutionary milestone in IBD, facilitating patient monitoring and the development of treat-to-target strategies using a simple blood marker.

Several miRNAs act on the same signaling pathways that are targets of drugs used to treat IBD[13,20-24], suggesting the potential use of miRNAs as IBD targets. The modulation of these miRNAs may positively interfere with patient responses to treatment, which is a promising strategy for drug development, as previously reported for miR-29[21], miR-155[22], and miR-126[23].

Regarding the modulation of miRNAs as a therapeutic strategy, a clinical trial is evaluating the efficacy of the small molecule drug candidate obefazimod for the treatment of moderate to severe active UC[35]. Obefazimod is the only known molecule that modulates miRNAs, as it enhances miR-124 expression, which is responsible for modulating inflammation and the innate immune response activated in IBD[35]. Results from this clinical trial are expected soon. Considering this mechanism of action, future studies should include other miRNAs as therapeutic targets; for example, the activation of miRNAs that help maintain the intestinal barrier, including miR-200 and miR-93, or inhibition of miRNAs that negatively regulate inflammatory processes, including miR-223 and miR-320a, should be evaluated.

In addition to their potential use as diagnostic markers and therapeutic targets, miRNAs have been studied as predictors of clinical and endoscopic responses in IBD patients. Reduced serum expression levels of let-7e at week 14 and miR-126 at week 54 were associated with clinical remission at weeks 14 and 54 and endoscopic remission at week 54 in 37 patients with CD treated with anti-tumor necrosis factor α therapy[36]. Another study found that increased let-7d and let-7e expression were associated with clinical remission at week 14 after infliximab induction therapy in CD, suggesting that these miRNAs are possible therapeutic biomarkers in CD patients treated with infliximab[37].

In severe acute colitis, a study evaluated tissue miRNAs associated with the response to intravenous (IV) steroids and in response to infliximab or cyclosporine in steroid-refractory patients[13]. Initially, 15 miRNAs associated with the response to IV steroids were identified (hp_hsa-mir-3934, hp_hsamir-3667, hp_hsa-mir-100, hsa-miR-603, hsa-miR-718, hsa-miR-4259, hp_hsa-mir-193b, hsa-miR-3150a-5p, hp_hsa-mir-1260b, hsa-miR-938, hsa-miR-3128, hsa-miR-4423-3p, hsa-miR-518b, hsa-miR-1468, and hsa-miR-3152-3p), in addition to six miRNAs associated with the response to infliximab

Table 1 Roles of microRNAs in patients with inflammatory bowel disease

What is already known about miRNAs in IBD?	What can we expect from miRNAs in IBD?	Ref.
Regulate cellular processes and homeostasis	Discover new functions in the pathophysiology of IBD	[8-11]
Differentially expressed between patients with IBD and healthy controls	Can be used as diagnostic markers for IBD	[5,6,16-19]
Differentially expressed between UC and CD	Can be used to differentiate UC from CD	[6]
Differentially expressed with respect to disease activity	Can be used as biomarkers of inflammatory activity	[16,17,19,32]
Regulated in response to drug exposure	Can be used as markers of drug responses	[20]
Regulate the expression of inflammatory cytokines	Potential therapeutic targets in IBD	[21,22,23]
Act on the intestinal barrier	Potential therapeutic targets in IBD	[25,26]
Modulate the intestinal microbiota	Potential therapeutic targets in IBD	[27-29]

CD: Crohn’s disease; IBD: Inflammatory bowel disease; miRNA: microRNA; UC: Ulcerative colitis.

Table 2 Barriers to the use of microRNAs in clinical practice

High exam cost
Better definition of miRNAs as diagnostic markers in IBD (differentiation between UC and CD and diagnosis of disease activity)
Few validation studies of miRNAs as blood, fecal, and endoscopic biomarkers
Better definition of the differences between the expression of fecal, blood, and tissue miRNAs
Lack of evidence validating miRNAs as a tool for evaluating mucosal healing
Lack of evidence validating miRNAs as a tool for evaluating histological remission
Lack of evidence validating miRNAs predictors of clinical and endoscopic responses
Lack of evidence validating miRNAs in treatment monitoring
Lack of evidence validating miRNAs as predictors of severe disease
Insufficient data on the role of miRNAs in modulating the inflammatory response
Insufficient data on the effects of miRNAs on the intestinal barrier, intestinal microbiota, and the response to probiotics

CD: Crohn’s disease; IBD: Inflammatory bowel disease; miRNA: microRNA; UC: Ulcerative colitis.

(hsa-miR-4423-3p, hsa-miR-3128, hsa-miR-3152-3p, hp_hsa-miR-193b, hsa-mi-R938, and hp_hsa-miR-100) and four miRNA associated with the ciclosporin response (hsa-mi-R4423-3p, hsa-mi-R938, hsa-mi-R518b, and hp_hsa-miR-100). In a validation cohort study, among the miRNAs initially identified, only two were significantly differentially expressed between responders and non-responders: miR-3934 for IV steroids and miR-938 for second-line treatment (infliximab or cyclosporine)[13].

In the pediatric population, five serum miRNAs (miR-126, let-7c, miR-146a, miR-146b, and miR-320a) were associated with the clinical response; further studies are needed to validate these miRNAs as biomarkers of infliximab and glucocorticoid treatment response within this specific population[38].

In the future, it will be important to consider the modulation of miRNAs by drugs or probiotics and the use of miRNAs as treatment itself (Table 1). A recent review has highlighted promising results in preclinical cancer studies when using a single miRNA to target multiple genes[39]. Despite these advances, several limitations and challenges must be overcome to enable the use of miRNAs in IBD in clinical practice, as described in Table 2.

CONCLUSION

Previous studies have demonstrated that miRNAs are important mediators of the inflammatory process in IBD patients and represent potential therapeutic targets for the development of new drugs. Experimental and clinical studies have focused on the modulation of miRNA expression, either by stimulating miRNA expression with anti-inflammatory functions or inhibiting miRNA expression with pro-inflammatory functions. In this editorial, we present the main findings and future perspectives regarding miRNAs and their roles in IBD patients. Currently, there is no specific miRNA biomarker for IBD, nor is there a specific marker for UC or CD. It is expected that in the future, miRNAs will be developed as sensitive and specific diagnostic, therapeutic, and prognostic biomarkers in IBD, providing a non-invasive

and accessible tool for effective monitoring.

FOOTNOTES

Author contributions: de Oliveira ECS, Quaglio AEV, Grillo TG, Di Stasi LC, and Sasaki LY contributed equally to the conception and design of the article, writing, and editing the manuscript, and review of the literature; All the authors approved the final version of the article to be published.

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