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## TOPIC HIGHLIGHT

### 2015 Advances in Inflammatory Bowel Disease

## MicroRNA in inflammatory bowel disease: Translational research and clinical implication

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### Abstract

Idiopathic inflammatory bowel disease (IBD) predominantly includes ulcerative colitis and Crohn's disease. The pathogenesis of IBD is complex and not

completely understood. MicroRNAs belong to a class of noncoding small RNAs that post-transcriptionally regulate gene expression. Unique microRNA expression profiles have been explored in IBD. In this review, we focus on the unique microRNA expression pattern in both tissue and peripheral blood from IBD patients and emphasize the potential diagnostic and therapeutic applications. The discovery of microRNAs has contributed to our understanding of IBD pathogenesis and might lead to clinical advance in new therapeutics.

**Key words:** Inflammatory bowel disease; Ulcerative colitis; Crohn's disease; MicroRNA; Pathogenesis; Gene expression

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**Core tip:** Idiopathic inflammatory bowel disease (IBD) predominantly includes ulcerative colitis and Crohn disease. The pathogenesis of IBD is complex and not completely understood. MicroRNAs belong to a class of noncoding small RNAs that post-transcriptionally regulate gene expression. Unique microRNA expression profiles have been explored in IBD. In this review, we focus on the unique microRNA expression pattern in both tissue and peripheral blood from IBD patients and emphasize the potential diagnostic and therapeutic applications. The discovery of microRNAs has contributed to our understanding of IBD pathogenesis and might lead to clinical advance in new therapeutics.

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## INTRODUCTION

Idiopathic inflammatory bowel disease (IBD) predominantly includes ulcerative colitis (UC) and Crohn's disease (CD), which is a chronic and recurrent inflammatory disorder primarily involving the gastrointestinal tract. The pathogenesis of IBD is multifactorial and not completely understood, but genetic, epigenetic, infectious, physiological, and immunological factors may all play important roles in the genesis and progression of the diseases<sup>[1-3]</sup>. So far, IBD is generally accepted as a complicated consequence attributable to inadequate immunological responses to luminal factors in genetically predisposed subjects.

MicroRNAs are encoded within the genomes of a wide variety of eukaryotes, including more than 700 different microRNA genes in the human genome<sup>[4,5]</sup>. MicroRNAs are evolutionarily conserved, single-stranded non-coding RNA molecules of 19–24 nucleotides, which represent a class of regulatory RNAs that decrease stability and suppress gene expression at a post-transcriptional level. MicroRNAs concurrently modulate the expression levels of dozens or more distinct messenger RNA (mRNA) targets. Alternatively, any given mRNA sequence may be targeted by several different microRNAs<sup>[4-6]</sup>. To date, they have been predicted to target and control the expression of at least 30% of the entire mammalian genome<sup>[7]</sup>. Since their discovery in 1933, microRNAs have been found to be involved in multiple pathophysiological networks<sup>[8,9]</sup> and in the pathogenesis of a broad-spectrum of human diseases, including cancer and inflammation<sup>[10-15]</sup>. Given their potential as therapeutic targets, microRNAs have drawn a lot of attention recently.

Knowledge of microRNA in IBD has accumulated in the past seven years and has indicated that microRNAs play critical roles in the pathogenesis of chronic inflammation and oncogenic transformation. Herein, the review focuses on the current understanding of microRNA as biomarkers of pathogenesis and potential therapeutic implication in IBD.

## DYSREGULATED MICRORNAS IN IBD

Multiple studies have demonstrated distinct microRNA expression profiles in tissue and peripheral blood of IBD patients. Many studies have been conducted on tissue and serum of patients with active or inactive IBD in an attempt to identify biomarkers and drivers of pathogenesis.

### **Aberrant microRNA profiles in mucosal tissue of UC**

Since 2008, dysregulated microRNAs have been identified by examining inflamed or uninfamed colonic tissue in UC patients<sup>[16-25]</sup>. As listed in Table 1, comparing to normal healthy controls aberrantly elevated microRNAs have been found including miR-7, miR-16, miR-20b, miR-21, miR-23a, miR-24, miR-29a,

miR-29b, miR-31, miR-98, miR-125b-1\*, miR-126, miR-126\*, miR-127-3p, miR-135b, miR-146a, miR-150, miR-155, miR-195, miR-196a, miR-206, miR-223, miR-324-3p, miR-375, miR-422b, miR-548a-3p, miR-650, miR-663, miR-let-7e\*, and miR-let-7f. The decreased microRNAs include miR-143, miR-145, miR-188-5p, miR-192, miR-194b, miR-196b, miR-215, miR-216b, miR-320a, miR-346, miR-375, miR-489, miR-548e, miR-559, and miR-630.

Given the variable anatomic location of colonic tissue, the diverse inflammatory status (either inflamed or uninfamed with or without treatment), the different cohorts of healthy control and analytical systems, it is not surprising that the findings are not consistent among researchers. However, three microRNA candidates, miR-21<sup>[16-18,24]</sup>, miR-29a<sup>[16,19]</sup> and miR-31<sup>[19,23]</sup>, have been found aberrantly elevated by at least two independent groups.

### **Aberrant microRNA profiles in mucosal tissue of CD**

As shown in Table 2, distinct microRNA expression profiles have also been studied in patients with CD<sup>[19,23,25-29]</sup>. MiR-9, miR-9\*, miR-16, miR-21, miR-22, miR-23b, miR-26a, miR-29b, miR-29c, miR-30a, miR-30b, miR-30c, miR-31, miR-34c-5p, miR-106a, miR-126, miR-126\*, miR-127-3p, miR-130a, miR-133b, miR-141, miR-146a, miR-146b-5p, miR-150, miR-155, miR-181c, miR-191, miR-196, miR-196a, miR-206, miR-223, miR-324-3p, miR-375, miR-594 and miR-663 have been found significantly increased comparing to the normal controls<sup>[19,23,26,28,29]</sup>. The decreased microRNAs include miR-7, miR-18a\*, miR-19b, miR-140-3p, miR-194b, miR-216b, miR-548e, miR-559, miR-629, miR-629\*, and miR-let-7b<sup>[23,27,30]</sup>.

Among them, miR-21<sup>[19,26]</sup>, miR-31<sup>[19,23,29]</sup>, miR-106a<sup>[19,26]</sup>, miR-146a<sup>[19,23]</sup>, and miR-223<sup>[19,26]</sup> have been found dysregulated by at least two independent groups.

### **Aberrant microRNA in peripheral blood of UC**

As summarized in Table 3, microRNA expression is also altered in the peripheral blood in patients with UC<sup>[24,25,31-34]</sup>. In studies examining microRNAs in peripheral blood mononuclear cells of patients with either active or inactive UC, miR-15b, miR-16, miR-19a, miR-20b\*, miR-21, miR-22, miR-24, miR-27a, miR-27a\*, miR-28-3p, miR-28-5p, miR-29a, miR-30e, miR-31, miR-92a-1\*, miR-93, miR-103, miR-103-2, miR-103-2\*, miR-128, miR-138, miR-140-3p, miR-142-5p, miR-143\*, miR-146a-3p, miR-150\*, miR-151-5p, miR-155, miR-181b, miR-188-5p, miR-196b, miR-199a-3p, miR-199a-5p, miR-221, miR-223, miR-330-3p, miR-340\*, miR-345, miR-362-3p, miR-362-5p, miR-374b, miR-378, miR-378\*, miR-422a, miR-423-5p, miR-500, miR-501-5p, miR-532-3p, miR-532-5p, miR-550\*, miR-598, miR-720, miR-760, miR-769-3p, miR-769-5p, miR-874, miR-941, miR-1271, miR-1274b, miR-1296, miR-let-7d, miR-

**Table 1** Aberrant microRNA expression in human colonic tissue in ulcerative colitis

Status	Tissue type	Control	Aberrant microRNA expression	Ref.
Active UC	Sigmoid, n = 15	Healthy	Decreased: miR-192 and 375 Increased: miR-16, 21, 23a, 24, 29a, 126, 195, 422b and let-7f	Wu <i>et al</i> <sup>[16]</sup> , 2008
		Healthy	Increased: miR-21 and 155	Takagi <i>et al</i> <sup>[17]</sup> , 2010
	Sigmoid, n = 12	Healthy	Increased: miR-21 and 126	Feng <i>et al</i> <sup>[18]</sup> , 2012
	Colon, nonspecific, n = 10	Healthy	Decreased: miR-188-5p, 215, 320a and 346 Increased: miR-7, 31, 135b and 223	Fasseu <i>et al</i> <sup>[19]</sup> , 2010
		Healthy	Increased: miR-150	Bian <i>et al</i> <sup>[20]</sup> , 2011
	Colon, nonspecific, n = 8	Healthy	Decreased: miR-143 and 145	Pekow <i>et al</i> <sup>[21]</sup> , 2012
Active or inactive UC	Colon, nonspecific, n = 20	Healthy	Increased: miR-20b, 98 and let-7e*	Coskun <i>et al</i> <sup>[22]</sup> , 2013
		Healthy	Decreased: miR-194b, 216b, 548e and 559 Increased: miR-31, 146a, 206 and 663	Lin <i>et al</i> <sup>[23]</sup> , 2014
Inactive UC	Sigmoid, n = 15	Healthy	Increased: miR-16, 23a, 24, 29a, 375 and 422b	Wu <i>et al</i> <sup>[16]</sup> , 2008
		Healthy	Decreased: miR-188-5p, 215, 320a and 346 Increased: miR-29a, 29b, 126*, 127-3p, 196a and 324-3p	Fasseu <i>et al</i> <sup>[19]</sup> , 2010
Unknown	Colon, nonspecific, n = 19	Healthy	Increased: miR-20b and 125b-1*	Coskun <i>et al</i> <sup>[22]</sup> , 2013
		Healthy	Increased: miR-21	Yang <i>et al</i> <sup>[24]</sup> , 2013
Active UC	Colon, nonspecific, n = 20	Inactive UC	Increased: miR-98	Coskun <i>et al</i> <sup>[22]</sup> , 2013
		Inactive UC	Decreased: miR-196b, 489 and 630 Increased: miR-548a-3p and 650	Iborra <i>et al</i> <sup>[25]</sup> , 2013

UC: Ulcerative colitis.

**Table 2** Aberrant microRNA expression in human colonic tissue in Crohn's disease

Status	Tissue type	Control	Aberrant microRNA expression	Ref.
Active CD	Sigmoid, n = 5	Healthy	Decreased: miR-19b and 629 Increased: miR-23b, 106a and 191	Wu <i>et al</i> <sup>[26]</sup> , 2010
		Healthy	Increased: miR-16, 21, 223, and 594	Wu <i>et al</i> <sup>[26]</sup> , 2010
	Colon, nonspecific, n = 16	Healthy	Increased: miR-9, 21, 22, 26a, 29b, 29c, 30b, 31, 34c-5p, 106a, 126, 126*, 127-3p, 130a, 133b, 146a, 146b-5p, 150, 155, 181c, 196a, 324-3p and 375	Fasseu <i>et al</i> <sup>[19]</sup> , 2010
		Healthy	Decreased: miR-7	Nguyen <i>et al</i> <sup>[27]</sup> , 2010
Active and inactive CD	Colon, nonspecific, n = 120	Healthy	Increased: miR-196	Brest <i>et al</i> <sup>[28]</sup> , 2011
		Healthy	Increased: miR-31 and 141	Huang <i>et al</i> <sup>[29]</sup> , 2015
	Colon, distalmost, n = 9	Healthy	Decreased: miR-194b, 216b, 548e and 559 Increased: miR-31, 146a, 206 and 663	Lin <i>et al</i> <sup>[23]</sup> , 2014
Inactive CD	Colon, nonspecific, n = 8	Healthy	Increased: miR-9*, 21, 22, 26a, 29b, 29c, 30a*, 30b, 30c, 31, 34c-5p, 106a, 126*, 127-3p, 133b, 146a, 146b-5p, 150, 155, 196a, 223 and 324-3p	Fasseu <i>et al</i> <sup>[19]</sup> , 2010
Active CD	Colon, left or sigmoid, n = 9	Inactive CD	Decreased: miR-18a*, 140-3p, 629* and let-7b Increased: miR-328, 422a and 885-5p	Iborra <i>et al</i> <sup>[25]</sup> , 2013

CD: Crohn's disease; UC: Ulcerative colitis.

let-7e, miR-let-7g, miR-let-7i\*, and miR-plus-E1271 are increasingly expressed comparing to the normal population<sup>[24,25,31-34]</sup>. The decreased profiles include miR-150 and miR-505\* comparing to the normal controls<sup>[25,31,33]</sup>.

Among them, nine microRNAs, miR-21<sup>[24,32]</sup>, miR-28-5p<sup>[31,32]</sup>, miR-151-5p<sup>[31,32]</sup>, miR-199a-5p<sup>[31,32]</sup>, miR-345<sup>[25,34]</sup>, miR-362-3p<sup>[31,33]</sup>, miR-505\*<sup>[31,33]</sup>, miR-532-3p<sup>[31,33]</sup> and miR-532-5p<sup>[25,34]</sup>, have been recognized by at least two independent groups.

#### Aberrant microRNA in peripheral blood of CD

As listed in Table 4, altered microRNA expression profiles are also found in the peripheral blood in patients with CD<sup>[25,31-33]</sup>. Compared to healthy controls, the increased microRNA profiles in the serum of patients with active CD include miR-16, miR-20a, miR-21, miR-23a, miR-27a\*, miR-29a, miR-30e,

miR-93, miR-106a, miR-107, miR-126, miR-140, miR-140-3p, miR-140-5p, miR-188-5p, miR-191, miR-192, miR-195, miR-199a-5p, miR-200c, miR-340\*, miR-362-3p, miR-484, miR-532-3p, miR-877, miR-plus-E1271, and miR-let-7b. The significantly decreased microRNAs consist of miR-18a, miR-128, miR-140-5p, miR-145, miR-149\*, miR-877, and miR-plus-F1065.

Among them, six microRNAs, including miR-16<sup>[25,32,33]</sup>, miR-106a<sup>[32,33]</sup>, miR-195<sup>[25,33]</sup>, miR-199a-5p<sup>[31,32]</sup>, miR-362-3p<sup>[31,32]</sup>, and miR-532-3p<sup>[31,32]</sup>, have been found by at least two independent groups.

#### MicroRNA as a differential biomarker to distinguish between UC and CD

As shown in Table 5, studies have shown that microRNAs are differentially expressed between UC and CD<sup>[19,31,35]</sup>. The panel of microRNAs that have been found differentially expressed in colonic tissue includes

**Table 3** Aberrant microRNA expression in human peripheral blood in ulcerative colitis

Status	Tissue type	Control	Aberrant microRNA expression	Ref.
Active UC	Peripheral blood, n = 13	Healthy	Decreased: miR-505* Increased: miR-28-5p, 103-2*, 151-5p, 199a-5p, 340*, 362-3p, 532-3p and plus-E1271	Wu <i>et al.</i> <sup>[31]</sup> , 2011
Active and inactive UC	Peripheral blood, n = 88	Healthy	Increased: miR-16, 21, 28-5p, 151-5p, 155 and 199a-5p	Paraskevi <i>et al.</i> <sup>[32]</sup> , 2012
	Peripheral blood, n = 18	Healthy	Decreased: miR-150 Increased: miR-15b, 19a, 24, 27a, 28-3p, 29a, 30e, 93, 103, 128, 142-5p, 196b, 199a-3p, 221, 223, 345, 374b, 423-5p, 532-5p, 598, 760, let-7d, let-7e and let-7g	Iborra <i>et al.</i> <sup>[25]</sup> , 2013
Inactive UC	Peripheral blood, n = 13	Healthy	Decreased: miR-505* Increased: miR-103-2, 362-3p and 532-3p	Zahm <i>et al.</i> <sup>[33]</sup> , 2011
Inactive UC	Peripheral blood, n = 10	Healthy	Decreased: miR-505* Increased: miR-103-2*, 362-3p and 532-3p	Wu <i>et al.</i> <sup>[31]</sup> , 2011
Unknown	Peripheral blood, n = 20	Healthy	Increased: miR-20b*, 22, 27a*, 31, 92a-1*, 138, 140-3p, 143*, 146a-3p, 150*, 181b, 188-5p, 330-3p, 362-5p, 345, 378, 378*, 422a, 500, 501-5p, 532-5p, 550*, 720, 769-3p, 769-5p, 874, 941, 1271, 1274b, 1296 and let-7i*	Dutta Gupta <i>et al.</i> <sup>[34]</sup> , 2012
	Peripheral blood, n = 15	Healthy	Increased: miR-21	Yang <i>et al.</i> <sup>[24]</sup> , 2013

UC: Ulcerative colitis.

**Table 4** Aberrant microRNA expression in human peripheral blood in Crohn's disease

Status	Tissue type	Control	Aberrant microRNA expression	Ref.
Active CD	Peripheral blood, n = 14	Healthy	Decreased: miR-149* and plus-F1065 Increased: miR-199a-5p, 340*, 362-3p, 532-3p and plus-E1271	Wu <i>et al.</i> <sup>[31]</sup> , 2011
	Peripheral blood, n = 46	Healthy	Increased: miR-16, 20a, 21, 30e, 93, 106a, 140, 192, 195, 484 and let-7b	Zahm <i>et al.</i> <sup>[33]</sup> , 2011
Active and inactive CD	Peripheral blood, n = 128	Healthy	Increased: miR-16, 23a, 29a, 106a, 107, 126, 191, 199a-5p, 200c, 362-3p and 532-3p	Paraskevi <i>et al.</i> <sup>[32]</sup> , 2012
		Healthy	Decreased: miR-877 Increased: miR-16, 27a*, 140-3p, 140-5p and 195	Iborra <i>et al.</i> <sup>[25]</sup> , 2013
Inactive CD	Peripheral blood, n = 5	Healthy	Decreased: miR-149* Increased: miR-340*	Wu <i>et al.</i> <sup>[31]</sup> , 2011
Active CD	Peripheral blood, n = 9	Inactive CD	Decreased: miR-18a, 128, 140-5p and 145 Increased: miR-188-5p and 877	Iborra <i>et al.</i> <sup>[25]</sup> , 2013

CD: Crohn's disease; UC: Ulcerative colitis.

**Table 5** Differential microRNA expression between ulcerative colitis and Crohn's disease

Status	Tissue type	Control	Aberrant microRNA expression	Ref.
Inactive UC	Colon, nonspecific, n = 8	Inactive CD	Decreased: miR-100a-3p, 100b-5p, 150, 196b, 223 and 320a	Fasseu <i>et al.</i> <sup>[19]</sup> , 2010
Active or inactive UC	Colon, distalmost, n = 12	Active or Inactive CD	Increased: miR-19b, 23b, 106a, 191 and 629	Lin <i>et al.</i> <sup>[35]</sup> , 2013
		Active CD	Increased: miR-3180-3p, plus-E1035 and plus-F1159	Wu <i>et al.</i> <sup>[31]</sup> , 2011

CD: Crohn's disease; UC: Ulcerative colitis.

miR-19b, miR-23b, miR-100a-3p, miR-100b-5p, miR-106a, miR-150, miR-191, miR-196b, miR-223, miR-320a, and miR-629<sup>[19,35]</sup>. Wu and colleagues found three microRNAs (miR-3180-3p, miR-plus-E1035 and miR-plus-F1159) differentially expressed in the peripheral blood between UC and CD<sup>[31]</sup>. Although at least two groups have developed tissue microRNA panels that attempted to delineate between UC and CD, there is little overlap. Importantly, these studies vary in the activity status of IBD during sampling, which may explain the differences seen by independent groups.

### MicroRNA in indeterminate IBD

A diagnosis of idiopathic IBD requires comprehensive analysis of clinical, radiographic, endoscopic, surgical, and histologic data. While most cases of IBD can be specifically classified as either UC or CD, 5%-10% of IBD patients bear equivocal features, falling into the category of indeterminate colitis<sup>[36-38]</sup>. The ability to better classify cases of indeterminate colitis would allow for better clinical and surgical management of these patients, especially regarding the choice of pouch procedure.

In a study by Lin and colleagues, a panel of miR-



19b, miR-23b, miR-106a, miR-191 and miR-629, was evaluated in 16 patients with clinical diagnosis of indeterminate colitis. They found that 15 patients demonstrated UC-like and one CD-like microRNA expression patterns<sup>[35]</sup>. They concluded that microRNA expression pattern in indeterminate colitis are far more similar to those of UC than CD. The study of microRNA expression pattern in indeterminate colitis provides molecular evidence indicating that most indeterminate colitis are probably UC, rather than CD, which is similar to the data from long-term clinical follow-ups. Molecular testing using microRNA as promising markers to improve the classification of indeterminate IBD has the considerable advantage of being testable at the time of colectomy for improved pouch surgery selection. Before being used as a clinically validate test, clinical validation in large samples of indeterminate colitis patients, especially with correlation to pouch prognosis, is a necessity.

## MICRORNA AS A POTENTIAL DRIVER OF PATHOGENESIS

Despite the heterogeneity of microRNAs identified as deregulated in IBD, a few microRNAs confirm in multiple studies and may represent causative agents in disease development. Here we focus on the microRNA with the best evidence as driver of pathogenesis.

### *MiR-21 potentiates disease severity in IBD*

As discussed above, miR-21 has been identified as being upregulated in active UC and CD, consistent with its possible role in the pathogenesis of IBD<sup>[16-18,24]</sup>. *In vitro* experiments have shown that the genetic deletion of DNMT1 and DNMT3b caused dysregulation of approximately 10% of microRNAs, demonstrating tight regulation by DNA methylation<sup>[39]</sup>. The use of microarray and confirmatory pyrosequencing have shown the miR-21 locus is hypomethylated, and therefore overexpressed, in samples of peripheral blood in active CD in pediatric and adult patients<sup>[40]</sup>. To determine if miR-21 was a potential driver of IBD pathogenesis, a miR-21 knockout mouse model was developed and treated with dextran sodium sulphate (DSS) to induce a chronic colitis model with an elevation of tumor necrosis factor alpha (TNF- $\alpha$ ) that mimics human IBD<sup>[41]</sup>. In wild type mice, the addition of DSS caused a significant increase in miR-21 levels, a dramatic reduction in weight, and significant mortality while the miR-21 knockout mice were resistant to these negative effects, which supports a role of miR-21 in IBD pathogenesis.

The pathogenic effects of miR-21 overexpressing are thought to be mediated through at least 3 separate mechanisms. First, miR-21 is thought to cause increased intestinal permeability, a factor thought to initiate IBD. At baseline, no difference in intestinal permeability was seen between wild type and miR-21

knockout mice<sup>[41]</sup>. After treatment with DSS, intestinal permeability was greater in wild type mice than that of miR-21 knockout strain. Secondly, miR-21 is pro-apoptotic. Although the mechanism has not been elucidated, miR-21 knockout mice treated with DSS had less intestinal epithelial cell apoptosis<sup>[41]</sup>. Prevention of epithelial cell apoptosis may help maintain the epithelial cell barrier and limit inflammation and disease progression. Thirdly, interstitial fibrosis is a hallmark of IBD and miR-21 has been associated with fibrosis in multiple disease models. Mouse models of renal fibrosis have shown that cellular injury leads to increased levels of TNF- $\alpha$  and subsequent induction of miR-21<sup>[42]</sup>. Inhibition of miR-21 prevented fibrosis, presumably through preventing the recruitment of pro-fibrotic inflammatory cells<sup>[42]</sup>. Increased serum levels of miR-21 were seen in humans with idiopathic pulmonary fibrosis and may serve as a non-invasive biomarker for disease progression<sup>[43]</sup>. Analysis of serum and hepatic tissue from patients with cirrhosis has also shown that increased miR-21 levels are associated with levels of fibrosis<sup>[44]</sup>. Although miR-21 has not been experimentally linked to fibrosis in IBD yet, its role deserves further study. Interestingly, miR-21 expression was found to be high in IBD-associated dysplasia suggesting that its expression is maintained throughout the development of dysplasia and carcinogenesis, but more controlled studies are needed to define its role<sup>[45]</sup>.

## MICRORNA AS A POTENTIAL BIOMARKER FOR CARCINOGENESIS

Longstanding IBD is a well-known risk factor for colorectal cancer, although mechanisms of carcinogenesis are poorly unknown<sup>[46,47]</sup>. Studies have shown that the risk of IBD-associated colon cancer is related to the extent of the disease, severity of inflammation, and duration<sup>[48-50]</sup>. With chronic inflammation, colonic epithelium undergoes a transformation from inflamed, but not dysplastic to progressively dysplastic, and eventually to adenocarcinoma. Colonoscopies with surveillance biopsies for IBD-associated dysplasia are used to help guide surgical timing of colectomies. Although histologic examination can reproducibly identify dysplasia, IBD-associated dysplasia cannot be distinguished from sporadic dysplasia based on histologic appearance alone. Histologic examination of IBD-associated adenocarcinomas has characteristic features and demographics which may indicate a specific pathway to carcinogenesis<sup>[51]</sup>. Molecular alterations have been shown to lead to this histological progression<sup>[52-58]</sup>. Previous studies have demonstrated molecular abnormalities in normal-appearing non-dysplastic mucosa from patients with UC who had a remote dysplastic lesion<sup>[55-57,59-61]</sup>. Aneuploidy, chromosomal alterations, p53 mutation, loss of heterozygosity, and chromosome instability are present in

normal-appearing mucosa before the development of dysplasia<sup>[55-57,59-61]</sup>.

Studies of microRNAs may elucidate distinct pathways that may help reliably identified IBD-associated dysplasia and subsequent carcinogenesis. Recent studies demonstrate that microRNAs are largely involved in oncogenesis *via* their regulation of tumor suppressors and oncogenes<sup>[62]</sup>. In a study by Olaru *et al.*<sup>[63]</sup>, microRNA arrays were performed on tissue from eight patients with IBD-associated dysplasia. Twenty two microRNAs (miR-31, miR-31\*, miR-96, miR-135b, miR-141, miR-183, miR-192, miR-192\*, miR-194, miR-194\*, miR-200a, miR-200a\*, miR-200b, miR-200b\*, miR-200c, miR-203, miR-215, miR-224, miR-375, miR-424\*, miR-429, and miR-552) were significantly upregulated and 10 microRNAs (miR-122, miR-139-5p, miR-142-3p, miR-146b-5p, miR-155, miR-223, miR-490-2p, miR-501-5p, miR-892b, and miR-1288) were downregulated in dysplastic epithelium compared to the non-dysplastic inflamed tissue.

### **MiR-31 identifies IBD-associated dysplasia**

MiR-31 is upregulated in UC and CD, but not in other non-IBD colitis, such as microscopic colitis, that have no association with dysplasia or malignancy<sup>[64]</sup>. As early as 2007, miR-31 was found to be upregulated in sporadic colorectal adenocarcinomas<sup>[65-67]</sup>. However, the role of miR-31 in IBD-associated dysplasia or malignancy has only recently been examined. An assessment of the baseline miR-31 expression in normal tissue regardless the different anatomic locations of the colon allows for comparison of all colon specimens equally<sup>[63]</sup>. In addition, no difference of miR-31 expression level was seen between IBD-associated dysplasia and IBD-associated carcinomas. Importantly, the levels of miR-31 were found 11-fold higher in IBD-associated dysplasia or carcinoma when compared to that of IBD tissue without dysplasia<sup>[63]</sup>. Although in a smaller study set, these findings were not replicated and a link between microRNAs and p53 dysregulation was indicated<sup>[68]</sup>. Taken together, these findings suggest that miR-31 alteration might happen early in carcinogenesis and may be used a biomarker for IBD-associated dysplasia or malignancy.

## **MICRORNA AS POTENTIAL THERAPEUTIC TARGETS FOR IBD**

Understanding the underlying mechanisms that regulate gene expression and the complex interplay of factors is essential to develop novel therapeutics in IBD. The post-transcriptional regulation of gene expression is unique and is becoming increasingly important.

The ability of microRNAs to target multiple genes and biological signaling pathways has drawn great attention in potential clinical utility as innovative

therapeutic agents in treatment. Antisense oligonucleotides complementary to microRNAs, namely anti-microRNA oligonucleotides, can target specific microRNAs abolishing their function in *in vitro* cultured cells, or *in vivo* in animal models. For example in the achievement of cancer research, recent accumulating preclinical studies have shown the feasibility of slowing tumor progression by either overexpressing tumor suppressive microRNAs, or by neutralizing the activities of oncogenic microRNAs in cell- or animal-based cancer models<sup>[69-72]</sup>. In addition, a number of clinical drugs have shown to modulate the microRNA expression as anticancer effect *in vitro*<sup>[73,74]</sup>.

Particularly in the field of IBD, the mechanisms to modify microRNAs that might activate or inactivate pathways required for the inflammation progress are worth investigating. Potential therapeutic application targeted on microRNA is to block inflammatory progression to improve sensitivity to conventional therapies. The pharmacologic targeted tissue delivery consists of two general strategies: (1) antisense oligonucleotides complementary to specific mature microRNAs to inactivate the overexpressed pro-inflammatory process; and (2) to replace the expression of suppressive microRNAs.

To date, no therapeutic manipulation of microRNAs in IBD has been published in either cell lines or animal models yet. Although recent study has shown that inhibition of miR-21, a promising pathogenetic driver in IBD, slows the proliferation and progression in a nasopharyngeal carcinoma cell line<sup>[75]</sup>. The similar approach is expected to be tested in IBD cell line or animal model. Although side effects are another essential issue to be considered before an effective drug enters the markets, we can't help speculating that a new therapeutic concept, targeted microRNA drug for IBD, maybe emerges in the near future.

## **DILEMMAS**

During the past 7 years, the identification of microRNA in IBD has broadened our knowledge. However, the lack of a standardized approach often leads to inconsistent or even conflicting results.

The nomenclature for microRNA has continued to evolve since its discovery in 1993<sup>[8,9]</sup>. MicroRNAs were named in the order they were discovered, leading to identical microRNAs being given different names by different groups. As the microRNA field continues to expand, significant efforts have been made to clarify nomenclature using a unified system. Recent data added from deep genome sequencing has pushed the number of annotated microRNAs to roughly 1900 in the most recently nomenclature database, miRBase version 21<sup>[76]</sup>. The complicated historical nomenclature of microRNA makes literature evaluation difficult and diligent effort to confirm sequence identity of each in the literature must be made.

One of the most commonly encountered problems

is when we attempt to verify microRNA's role in IBD pathogenesis. Recent developments in microarrays have led to numerous attempts to identify microRNAs associated with a diverse set of disease processes. Despite the ability of candidate microRNAs to be validated by additional RT-PCR, there has been little reproducibility between groups. Differences in samples obtained from various anatomic locations, treatment regimens, and activity level of disease may account for discrepancies seen between studies. Additionally, microRNAs with the same sequence identity are given modifiers in their name based on their location within the genome. Most techniques do not distinguish microRNAs that have the same sequence but at different locations in the genome<sup>[76]</sup>. A more clear understanding of the genetic loci associated with microRNAs can provide insight into how they are regulated and become deregulated in pathogenesis.

## CONCLUSION

In summary, the accumulating knowledge of microRNA has significantly expanded our understanding of the pathogenesis of IBD and has demonstrated the usefulness of microRNAs as biomarkers with emerging clinical utility and the potential for personalized therapies.

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