HHS Public Access

Author manuscript

Curr Opin Gastroenterol. Author manuscript; available in PMC 2017 October 27.

Published in final edited form as:

Curr Opin Gastroenterol. 2016 July ; 32(4): 258–266. doi:10.1097/MOG.0000000000000284.

miRNAs: how many in IBD?

Jeremy S. Schaefer[1]

[1]Department of Diagnostic and Biomedical Sciences, The University of Texas Health Science Center at Houston School of Dentistry, Houston, TX, USA

Abstract

Purpose of review—MicroRNAs (miRNAs), small noncoding RNA molecules of approximately 22 nucleotides, have emerged as critical mediators of gene expression. As the dysregulation of gene expression can have far reaching impact on health and disease, miRNAs are being examined as potent new mediators of disease as either biomarkers or potential therapeutic targets. The purpose of this review is to evaluate the contribution of miRNAs to inflammatory bowel disease (IBD) pathophysiology.

Recent findings—Recent studies have evaluated the expression of miRNAs in tissue and body fluid specimens from patients with of the main subtypes of IBD -Crohn's disease (CD) and ulcerative colitis (UC). Unique miRNA expression patterns that may distinguish IBD subtypes have been uncovered.

Summary—Significant progress has been made in illuminating the complex interactive networks of miRNAs and gene targets in IBD. The potential use of miRNAs as disease biomarkers or therapeutics shows promise. However, there are still significant hurdles to overcome before miRNA-based therapeutics and diagnostics will be of clinical utility.

Keywords

inflammatory bowel disease; microRNAs; Crohn's disease; ulcerative colitis

Introduction

The inflammatory bowel diseases (IBD) are a group of chronic inflammatory conditions affecting the gastrointestinal tract. IBD is marked by periods of active disease flare-ups followed by remissions, either of which can last variable periods of time. While Crohn's disease (CD) and ulcerative colitis (UC) are the two major forms of IBD, there are a number of other less common forms of IBD, including indeterminate colitis and microscopic colitis. Whereas CD can affect any portion of the gastrointestinal tract and is commonly patchy with a transmural inflammatory pattern, UC is limited to the large intestine and has a continuous inflammatory pattern that involves only the mucosa. A commonality between CD and UC is

Correspondence to: Jeremy Schaefer, Department of Diagnostic and Biomedical Sciences, The University of Texas Health Science Center at Houston School of Dentistry, Behavioral & Biomedical Sciences Building, Suite 5314, 1941 East Rd, Houston, TX 77054, Jeremy.Schaefer@uth.tmc.edu, Tel: 713-486-4107, Fax: 713-486-0450.

Conflicts of interest

The authors have no conflicts of interest.

a dysregulated immune response in the intestine. Based on current evidence, IBD develops in genetically susceptible individuals due to complex interactions between environmental stimuli, the genome, the microbiome, and an inappropriate mucosal immune response. Genome wide association studies (GWAS) and linkage analyses have established a strong genetic component to IBD (stronger in CD than UC) with the identification of about 200 loci associated with the development of IBD [1–15]. However, this only accounts for 16–23% of the heritability of IBD [16–18]. Lack of concordance between twin siblings (one sibling is affected with IBD while the other is disease-free) has further established that other factors-epigenetics, epistasis, and environmental factors-influence the development of IBD [19–22]. This review will discuss some of the current findings regarding the role of microRNAs (miRNAs) in the pathophysiology of IBD and the outlook for miRNA-based diagnostics and therapeutics.

Overview of miRNAs

MicroRNAs are non-coding single stranded RNAs of 21–23 nucleotides derived from primary miRNA transcripts (pri-miRNA) of intergenic or intronic origin [23]. Originally discovered in the early 1990's, the first miRNA, Lin-4, regulates *Caenorhabditis elegans* development through repression of Lin-14 and Lin-28 [24,25]. Despite this observation, the significance of miRNAs continued to be largely underappreciated until the early 2000's when they were recognized as a distinct class of RNAs. Prior to 2002, when miRNAs were named the breakthrough of the year, there were less than 5oo miRNA publications. In 2015, as evidence of the import of miRNAs in health and disease, there were over 9000 miRNA publications in PubMed.

The primary function of miRNAs is to regulate gene expression at the post-transcriptional level. This begins with the biogenesis of miRNAs. miRNAs are transcribed as longer primary miRNAs (pri-miRNAs) of several hundred nucleotides from either a distinct gene or coupled to a host gene (e.g. intronic source). This distinction is important for regulatory mechanisms as the former will operate as its own transcriptional unit while the latter's transcription will be tied to that of the host protein coding gene. miRNA biogenesis occurs in a stepwise process using multiple RNA-binding proteins (DGCR8) and endoribonucleases (Drosha and Dicer). In the nucleus, the RNA-binding protein DGCR8 binds the RNA-specific endoribonuclease enzyme (ribonuclease type III) Drosha to form the microprocessor complex thereby initiating miRNA processing to cleave the pri-miRNA to the precursor miRNA (pre-miRNA) stem-loop structure. The pre-miRNA is exported to the cytoplasm where it undergoes further cleavage by Dicer ribonuclease to remove the stem loop. The active strand of the resulting miRNA:miRNA* duplex, of approximately 22 nucleotides in length, is incorporated into the RNA-induced silencing complex (RISC), a multisubunit complex composed of Argonaute proteins. The miRNA loaded RISC (miRISC) is now competent to induce gene silencing as the loaded miRNA provides specificity by binding to complimentary sequences on the target miRNA 3′ untranslated region (UTR). Gene silencing proceeds depending on this complementarity between the miRNA and its target mRNA: (i) mRNA degradation is favored with complete complementarity (primarily plants) [23], (ii) post-translational repression through mismatch binding of the 3′-UTR of the target gene, or (iii) mRNA destabilization via deadenylation of the poly(A) tail [23]. One of the

key features of miRNAs is their redundancy-a single miRNA can regulate multiple target genes and conversely, a single target gene will have multiple miRNAs with the potential to regulate it. This is one of the great challenges in miRNA research; defining which of the many miRNAs that may regulate a specific gene is the most important goal, particularly since many of the miRNA effects are relatively mild.

It is well established now that miRNAs play essential roles in the regulation of multiple vital developmental processes from cell differentiation and organogenesis to the fine-tuning of metabolic and physiochemical responses. As with such a large biological footprint, up to 60% of genes are targeted by miRNAs, abnormalities in miRNA expression could and do pose problems that contribute to the development of disease. Chronic lymphocytic leukemia was among the first human diseases associated with miRNA dysregulation, and dysregulated miRNA expression has since been found in numerous other disease states [26]. This applies to IBD, as there have been a number of recent studies examining the expression of miRNAs in IBD. Distinct miRNA expression patterns have been observed in intestinal biopsies, peripheral blood, and saliva.

Mucosal tissue miRNA expression

A number of studies have examined intestinal biopsies as a first step to define the miRNAs that are differentially expressed at the site of IBD pathology. The most common design for these studies was to compare patients with active CD or UC versus healthy controls. A few more recent studies have included subjects with inactive CD or UC as comparison groups. Other studies have examined the miRNA expression in biopsies from areas of active disease versus areas ostensibly normal by endoscopic appearance.

The formative studies into the role of miRNAs in IBD were pioneered by an initial study aimed primarily at delineating miRNAs linked to UC. In this study, Wu et al. compared intestinal biopsies from 15 healthy controls to 15 active UC and 15 inactive UC patients; microscopic colitis, irritable bowel syndrome, and CD patients were included in the analysis as well [27]. Among 11 miRNAs identified as having differential expression, miR-21 and miR-29a were found to have elevated expression in the active UC group while miR-192 expression was reduced [27]. Macrophage inflammatory peptide 2-α was identified as a regulatory target of miR-192 and its expression was found to have an inverse relationship with miR-192 [27]. A follow up study was performed in CD colitis and ileitis patients to identify colonic- and ileal-specific miRNAs, respectively. miR-23b, miR-191, and miR-106a were elevated while miR-19b and miR-629 were reduced in CD colitis [28]. miR-16, miR-21, miR-223, and miR-594 were elevated in CD ileitis [28]. Additional studies by Bian et al., Brest et al., Coskun et al., Fasseu et al., Feng et al., Lin et al., Min et al., Takagi et al., Yang et al., and others identified additional miRNAs with dysregulated expression in IBD in comparison to healthy controls (summarized in Tables 1 & 2).

More recent studies in the last year have identified or confirmed additional miRNAs. In a comparison of formalin-fixed paraffin-embedded or fresh-frozen colon biopsies, Béres and colleagues identified miR-146a and miR-155 as elevated in UC and CD patients [29]. Using RNA sequencing (RNA-seq), Peck et al. identified miR-31-5p, miR-215, and miR-223-3p as

elevated in CD while miR-203 was reduced [43]. Schaefer et al. identified miR-19a and miR-101 as additional miRNAs elevated in UC [47]. In contrast, Koukos et al. found miR-101 to be reduced in UC [37].

In a recent screen for novel regulators of nuclear factor kappa B (NF-κB) using miRNA inhibitors in human colonocytes, seven miRNAs (miR-7, miR-21, miR-146a, miR-181b, miR-214, miR-372, and miR-373) suppressed NF-κB phosphorylation and thus its activity [45]. In contrast, miRNA inhibitors for miR-26b and miR-199a promoted NF-κB phosphorylation and thus its activity [45]. When CD and UC colon biopsies were subsequently assayed for miRNA expression, miR-21 and miR-146a were elevated in both CD and UC while miR-214 was elevated only in UC [45]. PTEN and PDLIM2 were identified as targets of miR-214 and STAT3 as a transcriptional regulator of miR-214 expression [45].

Circulating miRNA expression

The development of an effective noninvasive and accurate test for disease has been a goal in the medical community for many diseases. This has been the case in the clinical diagnosis and treatment of IBD as well. Although endoscopic biopsies and histologic analysis remain the gold standard for diagnosing CD and UC, a number of less invasive tests are useful in the clinical management of IBD. Chief among these are fecal calprotectin levels and serum C-reactive protein levels. In an effort to improve the quality and accuracy of clinical tests of IBD, circulating miRNA expression has been explored as potential biomarkers of IBD. This is buoyed by several recent studies demonstrating that miRNAs exist in the peripheral blood, serum, and plasma in a stable RNase-resistant form [53,54].

Blood miRNA expression

An initial examination of peripheral blood miRNA expression in IBD patients relative to healthy controls revealed elevated expression of miR-199a-5p, miR-340-3p, miR-362-3p, and miR-532-3p in CD and UC [50]. miR-28-5p, miR-103-2-5p, and miR-151-5p were additionally elevated in UC while miR-505-5p and miR149-3p were reduced in UC and CD, respectively [50]. Duttagupta et al. analyzed miRNA expression after fractionating peripheral blood into microvesicle, peripheral blood mononuclear cell and platelet fractions [55]. Among 31 candidates within the platelet fraction, miR-188-5p, miR-422a, miR-378, miR-500, miR-501-55, miR-769-5p, and miR-874 were validated to have elevated expression in UC [55]. Zahm and colleagues identified 11 miRNAs with altered expression in pediatric CD (miR-16, let-7b, miR-195, miR-106a, miR-20a, miR-30e, miR-140, miR-484, miR-93, miR-192, and miR-21) [56]. Twelve miRNAs (miR-127-3p, miR-491-5p, miR-18a, miR-145, let-7b, miR-185, miR-29c, miR-19b, miR-20b, miR-106a, miR-17, and miR-222) were found to be elevated and one (miR-135a) reduced in serum in a study of CD and UC patients [57]. Paraskevi and colleagues reported eleven (miR-16, miR-23a, miR-29a, miR-106a, miR-107, miR-126, miR-191, miR-199a-5p, miR-200c, miR362-3p, and miR-532-3p) and five miRNAs (miR-16, miR-21, miR-28-5p, miR-151-5p, and miR-199a-5p) with elevated expression in CD and UC peripheral blood, respectively [42]. Another study examining the effects of anti-tumor necrosis factor-α (TNF-α) induction

therapy on miRNA expression in the serum of CD patients found elevated expression of let-7d, let-7e, miR-28-5p, miR-221, and miR-224 at week 6 of treatment [58]. Patients that were in remission by week 14 of therapy had elevated levels of let-7d and let-7e compared to non-responders [58]. Several recent studies found miR-223 to be elevated in the peripheral blood and serum of CD and UC patients [46,47,49]. Polytarchou and colleagues reported that serum miR-223-3p, miR-4454, miR23a-3p, and miR320e levels correlated with UC disease activity better than serum C-reactive protein levels [46]. Lewis et al. identified miR-19a-3p and miR-19b-3p as markers of stricturing CD, both miRNAs were expressed at lower levels in the serum of CD patients with strictures in comparison to non-stricturing CD patients [39].

Salivary miRNA expression

Evaluation of oral fluid (saliva) has become an intriguing diagnostic tool for many diseases due to its ease of accessibility. A recent study examining miRNA expression in saliva found that, in UC patients, salivary miRNA expression of miR-21, miR-31, and miR142-3p was elevated in comparison to healthy controls [47]. Salivary expression of miR-26a and miR-101 was elevated in CD [47].

miRNA targeting of IBD-associated genes

GWAS, next generation sequencing, and other studies have been instrumental in identifying IBD-susceptibility loci to help understand the complex genetic and biologic pathways underlying disease development [9]. The identification of dysregulated miRNAs in IBD, and their concomitant ability to regulate gene expression, has led to the exploration of the relationship of these miRNAs to these IBD loci. The primary strategies employed have either used IBD-associated miRNAs to search for downstream gene targets or used specific IBD-associated genes to identify regulatory miRNAs. Several laboratories employed the latter candidate gene approach to identify miR-93, miR-106b, miR130a, and miR142-3p as regulators of ATG16L1, one of the most common polymorphisms associated with CD [59–63]. Cognizant of the import of NF-κB as a mediator of inflammatory signals in UC, Polytarchou et al. performed a screen in colonocytes to identify miRNAs that altered NF-κB activity; PTEN and PDLIM2 were identified as targets of miR-214 as a result [45]. Through these efforts, a number of IBD-associated genes have been demonstrated to be targets of miRNAs, including genes involved in autophagy (ATG16L1), inflammation (TNF-α), intestinal homeostasis (IL12B), and cytokine production (STAT3) (Table 3).

Biologic therapies (primarily humanized monoclonal antibodies) directed against inflammatory mediators involved in the pathophysiology of IBD have revolutionized medical treatment. Tumor necrosis factor antagonists (adalimumab, certolizumab pegol, golimumab, infliximab), anti-cell adhesion molecule antibodies [natalizumab (anti-ITGA4 antibody) and vedolizumab (anti-LPAM-1 antibody)], and IL12p40 antagonists (ustekinumab) are either currently used for treating IBD [77–82]. While these biologics have the advantage of specificity in comparsion to glucocorticoids and other immunosuppressive agents (azathioprine, methotrexate), not all patients respond to these medications and some encounter significant side effects [77–83].

Thus, miRNA-based therapeutics could represent a significant alternative to these biologics. The potential of developing miRNAs to target IBD-associated genes is intriguing. However, there are several limitations that have yet to be solved in terms of miRNA-based therapeutics. To be successful, miRNA modulators must be specific, efficient, and safely deliverable to the affected tissue. Off-target side effects are still a major concern as altering the function of a single miRNA could affect many downstream gene targets and pathways. Site-specific delivery of miRNA therapeutics remains challenging.

Nevertheless, preclinical and clinical studies have demonstrated efficacy of miRNA-based therapeutics in cancer, hepatitis C virus infection, and heart disease [84–89]. MRX34, a liposomal injection of a miR-34a mimic, is being developed as a treatment for liver cancer (Mirna Therapeutics-NCT01829971) and has progressed to the clinical trial stage. A Phase 1 clinical study was recently initiated for MRG-201, a miRNA mimic to microRNA-29b, as an anti-fibrotic agent for cutaneous and pulmonary fibrosis (miRagen Therapeutics).

Several miRNA-based therapeutic studies have reported positive results in animal models of IBD. A study using the azoxymethane (AOM)-dextran sulfate sodium (DSS) mouse model of colitis-associated colorectal cancer development reported tumor suppression in groups treated with a chemical inhibitor (anti-miR) of miR-214 [45]. Anti-miR inhibition of miR-30c and miR-130a reduced intestinal inflammation in a mouse ileal loop model [60]. In IL-10 knockout mice and TNBS models of colitis, intestinal inflammation was exacerbated or reduced after intracolonic administration of an anti-miR (for inhibition) or pre-miR miRNA mimic (for overexpression) to miR-141, respectively [90]. Overexpression of miR-146b ameliorated intestinal inflammation in DSS-treated mice [91].

Conclusion

While the exact biological mechanisms are not well understood, it is undeniable that miRNAs play a significant role in the pathogenesis of IBD. This leads to several important conclusions. The first is that several miRNAs were consistently altered across multiple studies reinforcing the import of these miRNAs in IBD. Second, these studies underscore the promise of miRNAs as biomarkers for diagnosing and monitoring disease activity in IBD as well as the potential of miRNA-based therapeutics. Future areas of investigation include continued improvement and refinement of miRNA diagnostics and therapeutics and identification of polymorphisms that impact miRNA binding sites.

Acknowledgments

None.

Financial support and sponsorship

This work has been supported by NIH grants Center Grant P30 DK56338, a Career Development Award from the Crohn’s & Colitis Foundation of America (CCFA), and an Institution-funded CCTS/KL2 career development grant.

References

1. Baptista ML, Amarante H, Picheth G, Sdepanian VL, Peterson N, Babasukumar U, Lima HC, Kugathasan S. CARD15 and IL23R influences Crohn's disease susceptibility but not disease phenotype in a Brazilian population. Inflamm Bowel Dis. 2008; 14:674–679. [PubMed: 18200510]
2. Bouzid D, Amouri A, Fourati H, Marques I, Abida O, Tahri N, Goncalves CP, Masmoudi H. Polymorphisms in the IL2RA and IL2RB genes in inflammatory bowel disease risk. Genet Test Mol Biomarkers. 2013; 17:833–839. [PubMed: 23972291]
3. Cho JH, Brant SR. Recent insights into the genetics of inflammatory bowel disease. Gastroenterology. 2011; 140:1704–1712. [PubMed: 21530736]
4. Fowler EV, Doecke J, Simms LA, Zhao ZZ, Webb PM, Hayward NK, Whiteman DC, Florin TH, Montgomery GW, Cavanaugh JA, et al. ATG16L1 T300A shows strong associations with disease subgroups in a large Australian IBD population: further support for significant disease heterogeneity. Am J Gastroenterol. 2008; 103:2519–2526. [PubMed: 18671817]
5. Fujino S, Andoh A, Bamba S, Ogawa A, Hata K, Araki Y, Bamba T, Fujiyama Y. Increased expression of interleukin 17 in inflammatory bowel disease. Gut. 2003; 52:65–70. [PubMed: 12477762]
6. Glas J, Seiderer J, Bues S, Stallhofer J, Fries C, Olszak T, Tsekeri E, Wetzke M, Beigel F, Steib C, et al. IRGM variants and susceptibility to inflammatory bowel disease in the German population. PLoS One. 2013; 8:e54338. [PubMed: 23365659]
7. Hayatbakhsh MM, Zahedi MJ, Shafiepour M, Nikpoor AR, Mohammadi M. IL-23 receptor gene rs7517847 and rs1004819 SNPs in ulcerative colitis. Iran J Immunol. 2012; 9:128–135. [PubMed: 22735800]
8. Hong SN, Park C, Park SJ, Lee CK, Ye BD, Kim YS, Lee S, Chae J, Kim JI, Kim YH, et al. Deep resequencing of 131 Crohn's disease associated genes in pooled DNA confirmed three reported variants and identified eight novel variants. Gut. 2015
9*. McGovern DP, Kugathasan S, Cho JH. Genetics of Inflammatory Bowel Diseases. Gastroenterology. 2015; 149:1163–1176. e1162. An important review summarizing the current status of genetic loci linked to IBD. [PubMed: 26255561]
10. Moran CJ, Walters TD, Guo CH, Kugathasan S, Klein C, Turner D, Wolters VM, Bandsma RH, Mouzaki M, Zachos M, et al. IL-10R polymorphisms are associated with very-early-onset ulcerative colitis. Inflamm Bowel Dis. 2013; 19:115–123. [PubMed: 22550014]
11. Roberts RL, Gearry RB, Hollis-Moffatt JE, Miller AL, Reid J, Abkevich V, Timms KM, Gutin A, Lanchbury JS, Merriman TR, et al. IL23R R381Q and ATG16L1 T300A are strongly associated with Crohn's disease in a study of New Zealand Caucasians with inflammatory bowel disease. Am J Gastroenterol. 2007; 102:2754–2761. [PubMed: 17894849]
12. Salem M, Ammitzboell M, Nys K, Seidelin JB, Nielsen OH. ATG16L1: A multifunctional susceptibility factor in Crohn disease. Autophagy. 2015; 11:585–594. [PubMed: 25906181]
13. Torok HP, Glas J, Endres I, Tonenchi L, Teshome MY, Wetzke M, Klein W, Lohse P, Ochsenkuhn T, Folwaczny M, et al. Epistasis between Toll-like receptor-9 polymorphisms and variants in NOD2 and IL23R modulates susceptibility to Crohn's disease. Am J Gastroenterol. 2009; 104:1723–1733. [PubMed: 19455129]
14. Tremelling M, Cummings F, Fisher SA, Mansfield J, Gwilliam R, Keniry A, Nimmo ER, Drummond H, Onnie CM, Prescott NJ, et al. IL23R variation determines susceptibility but not disease phenotype in inflammatory bowel disease. Gastroenterology. 2007; 132:1657–1664. [PubMed: 17484863]
15. Yamazaki K, McGovern D, Ragoussis J, Paolucci M, Butler H, Jewell D, Cardon L, Takazoe M, Tanaka T, Ichimori T, et al. Single nucleotide polymorphisms in TNFSF15 confer susceptibility to Crohn's disease. Hum Mol Genet. 2005; 14:3499–3506. [PubMed: 16221758]
16. Anderson CA, Boucher G, Lees CW, Franke A, D'Amato M, Taylor KD, Lee JC, Goyette P, Imielinski M, Latiano A, et al. Meta-analysis identifies 29 additional ulcerative colitis risk loci, increasing the number of confirmed associations to 47. Nat Genet. 2011; 43:246–252. [PubMed: 21297633]

17. Franke A, McGovern DP, Barrett JC, Wang K, Radford-Smith GL, Ahmad T, Lees CW, Balschun T, Lee J, Roberts R, et al. Genome-wide meta-analysis increases to 71 the number of confirmed Crohn's disease susceptibility loci. Nat Genet. 2010; 42:1118–1125. [PubMed: 21102463]

18. Khor B, Gardet A, Xavier RJ. Genetics and pathogenesis of inflammatory bowel disease. Nature. 2011; 474:307–317. [PubMed: 21677747]

19. Petersen BS, Spehlmann ME, Raedler A, Stade B, Thomsen I, Rabionet R, Rosenstiel P, Schreiber S, Franke A. Whole genome and exome sequencing of monozygotic twins discordant for Crohn's disease. BMC Genomics. 2014; 15:564. [PubMed: 24996980]

20. Picco MF. Share and share alike? Twins and environmental risk factors for inflammatory bowel disease. Inflamm Bowel Dis. 2006; 12:934–935. [PubMed: 17012963]

21. Spehlmann ME, Begun AZ, Burghardt J, Lepage P, Raedler A, Schreiber S. Epidemiology of inflammatory bowel disease in a German twin cohort: results of a nationwide study. Inflamm Bowel Dis. 2008; 14:968–976. [PubMed: 18253950]

22. Spehlmann ME, Begun AZ, Saroglou E, Hinrichs F, Tiemann U, Raedler A, Schreiber S. Risk factors in German twins with inflammatory bowel disease: results of a questionnaire-based survey. J Crohns Colitis. 2012; 6:29–42. [PubMed: 22261525]

23. Lin SL, Miller JD, Ying SY. Intronic MicroRNA (miRNA). J Biomed Biotechnol. 2006; 2006:26818. [PubMed: 17057362]

24. Lee RC, Feinbaum RL, Ambros V. The C. elegans heterochronic gene lin-4 encodes small RNAs with antisense complementarity to lin-14. Cell. 1993; 75:843–854. [PubMed: 8252621]

25. Wightman B, Ha I, Ruvkun G. Posttranscriptional regulation of the heterochronic gene lin-14 by lin-4 mediates temporal pattern formation in C. elegans. Cell. 1993; 75:855–862. [PubMed: 8252622]

26. Calin GA, Ferracin M, Cimmino A, Di Leva G, Shimizu M, Wojcik SE, Iorio MV, Visone R, Sever NI, Fabbri M, et al. A MicroRNA signature associated with prognosis and progression in chronic lymphocytic leukemia. N Engl J Med. 2005; 353:1793–1801. [PubMed: 16251535]

27. Wu F, Zikusoka M, Trindade A, Dassopoulos T, Harris ML, Bayless TM, Brant SR, Chakravarti S, Kwon JH. MicroRNAs are differentially expressed in ulcerative colitis and alter expression of macrophage inflammatory peptide-2 alpha. Gastroenterology. 2008; 135:1624–1635. e1624. [PubMed: 18835392]

28. Wu F, Zhang S, Dassopoulos T, Harris ML, Bayless TM, Meltzer SJ, Brant SR, Kwon JH. Identification of microRNAs associated with ileal and colonic Crohn's disease. Inflamm Bowel Dis. 2010; 16:1729–1738. [PubMed: 20848482]

29*. Beres NJ, Szabo D, Kocsis D, Szucs D, Kiss Z, Muller KE, Lendvai G, Kiss A, Arato A, Sziksz E, et al. Role of Altered Expression of miR-146a, miR-155, and miR-122 in Pediatric Patients with Inflammatory Bowel Disease. Inflamm Bowel Dis. 2016; 22:327–335. This study assesses miRNA expression in pediatric patients with IBD. [PubMed: 26752469]

30. Bian Z, Li L, Cui J, Zhang H, Liu Y, Zhang CY, Zen K. Role of miR-150-targeting c-Myb in colonic epithelial disruption during dextran sulphate sodium-induced murine experimental colitis and human ulcerative colitis. J Pathol. 2011; 225:544–553. [PubMed: 21590770]

31. Brest P, Lapaquette P, Souidi M, Lebrigand K, Cesaro A, Vouret-Craviari V, Mari B, Barbry P, Mosnier JF, Hebuterne X, et al. A synonymous variant in IRGM alters a binding site for miR-196 and causes deregulation of IRGM-dependent xenophagy in Crohn's disease. Nat Genet. 2011; 43:242–245. [PubMed: 21278745]

32*. Cheng X, Zhang X, Su J, Zhang Y, Zhou W, Zhou J, Wang C, Liang H, Chen X, Shi R, et al. miR-19b downregulates intestinal SOCS3 to reduce intestinal inflammation in Crohn's disease. Sci Rep. 2015; 5:10397. This study identified SOCS3 as a target of miR-19b and reported efficacy of a miR-19b-based therapeutic in the TNBS mouse model of colitis. [PubMed: 25997679]

33. Coskun M, Bjerrum JT, Seidelin JB, Troelsen JT, Olsen J, Nielsen OH. miR-20b, miR-98, miR-125b-1*, and let-7e* as new potential diagnostic biomarkers in ulcerative colitis. World J Gastroenterol. 2013; 19:4289–4299. [PubMed: 23885139]

34. Fasseu M, Treton X, Guichard C, Pedruzzi E, Cazals-Hatem D, Richard C, Aparicio T, Daniel F, Soule JC, Moreau R, et al. Identification of restricted subsets of mature microRNA abnormally

expressed in inactive colonic mucosa of patients with inflammatory bowel disease. PLoS One. 2010:5.

35. Feng X, Wang H, Ye S, Guan J, Tan W, Cheng S, Wei G, Wu W, Wu F, Zhou Y. Up-regulation of microRNA-126 may contribute to pathogenesis of ulcerative colitis via regulating NF-kappaB inhibitor IkappaBalpha. PLoS One. 2012; 7:e52782. [PubMed: 23285182]

36*. He C, Shi Y, Wu R, Sun M, Fang L, Wu W, Liu C, Tang M, Li Z, Wang P, et al. miR-301a promotes intestinal mucosal inflammation through induction of IL-17A and TNF-alpha in IBD. Gut. 2015 This study reported that miR-301a overexpression promoted Th17 cell differentiation and TNF-α production.

37. Koukos G, Polytarchou C, Kaplan JL, Morley-Fletcher A, Gras-Miralles B, Kokkotou E, Baril-Dore M, Pothoulakis C, Winter HS, Iliopoulos D. MicroRNA-124 regulates STAT3 expression and is down-regulated in colon tissues of pediatric patients with ulcerative colitis. Gastroenterology. 2013; 145:842–852. e842. [PubMed: 23856509]

38*. Koukos G, Polytarchou C, Kaplan JL, Oikonomopoulos A, Ziring D, Hommes DW, Wahed R, Kokkotou E, Pothoulakis C, Winter HS, et al. A microRNA signature in pediatric ulcerative colitis: deregulation of the miR-4284/CXCL5 pathway in the intestinal epithelium. Inflamm Bowel Dis. 2015; 21:996–1005. This study reported an inverse relationship between miR-4284 and CXCL5 mRNA expression with pediatric UC patients having reduced miR-4284 expression. [PubMed: 25738378]

39*. Lewis A, Mehta S, Hanna LN, Rogalski LA, Jeffery R, Nijhuis A, Kumagai T, Biancheri P, Bundy JG, Bishop CL, et al. Low Serum Levels of MicroRNA-19 Are Associated with a Stricturing Crohn's Disease Phenotype. Inflamm Bowel Dis. 2015; 21:1926–1934. This study identified a correlation between the serum levels of miR-19a/miR-19b and the propensity for the stricturing phenotype in CD patients. [PubMed: 25985247]

40. Lin J, Welker NC, Zhao Z, Li Y, Zhang J, Reuss SA, Zhang X, Lee H, Liu Y, Bronner MP. Novel specific microRNA biomarkers in idiopathic inflammatory bowel disease unrelated to disease activity. Mod Pathol. 2014; 27:602–608. [PubMed: 24051693]

41. Min M, Peng L, Yang Y, Guo M, Wang W, Sun G. MicroRNA-155 is involved in the pathogenesis of ulcerative colitis by targeting FOXO3a. Inflamm Bowel Dis. 2014; 20:652–659. [PubMed: 24583476]

42. Paraskevi A, Theodoropoulos G, Papaconstantinou I, Mantzaris G, Nikiteas N, Gazouli M. Circulating MicroRNA in inflammatory bowel disease. J Crohns Colitis. 2012; 6:900–904. [PubMed: 22386737]

43*. Peck BC, Weiser M, Lee SE, Gipson GR, Iyer VB, Sartor RB, Herfarth HH, Long MD, Hansen JJ, Isaacs KL, et al. MicroRNAs Classify Different Disease Behavior Phenotypes of Crohn's Disease and May Have Prognostic Utility. Inflamm Bowel Dis. 2015; 21:2178–2187. An important study that attempts to correlate miRNA expression profiles with specific phenotypes/disease behaviors of CD. [PubMed: 26164662]

44*. Pierdomenico M, Cesi V, Cucchiara S, Vitali R, Prete E, Costanzo M, Aloi M, Oliva S, Stronati L. NOD2 Is Regulated By Mir-320 in Physiological Conditions but this Control Is Altered in Inflamed Tissues of Patients with Inflammatory Bowel Disease. Inflamm Bowel Dis. 2016; 22:315–326. This study estabishes NOD2 as a target of miR-320 regulation. [PubMed: 26752466]

45**. Polytarchou C, Hommes DW, Palumbo T, Hatziapostolou M, Koutsioumpa M, Koukos G, van der Meulen-de Jong AE, Oikonomopoulos A, van Deen WK, Vorvis C, et al. MicroRNA214 Is Associated With Progression of Ulcerative Colitis, and Inhibition Reduces Development of Colitis and Colitis-Associated Cancer in Mice. Gastroenterology. 2015; 149:981–992. e911. An important study that identifies miR-214 as a specific biomarker for UC nd reported efficacy of a miR-214-based therapeutic in the AOM-DSS mouse model of colitis associated cancer. [PubMed: 26055138]

46*. Polytarchou C, Oikonomopoulos A, Mahurkar S, Touroutoglou A, Koukos G, Hommes DW, Iliopoulos D. Assessment of Circulating MicroRNAs for the Diagnosis and Disease Activity Evaluation in Patients with Ulcerative Colitis by Using the Nanostring Technology. Inflamm Bowel Dis. 2015; 21:2533–2539. An important study that compared serum microRNA

expression with C-reactive protein (CRP) levels to estimate UC disease activity. [PubMed: 26313695]

47*. Schaefer JS, Attumi T, Opekun AR, Abraham B, Hou J, Shelby H, Graham DY, Streckfus C, Klein JR. MicroRNA signatures differentiate Crohn's disease from ulcerative colitis. BMC Immunol. 2015; 16:5. This study reported the differential expression of miRNAs in the saliva of IBD patients. [PubMed: 25886994]

48. Takagi T, Naito Y, Mizushima K, Hirata I, Yagi N, Tomatsuri N, Ando T, Oyamada Y, Isozaki Y, Hongo H, et al. Increased expression of microRNA in the inflamed colonic mucosa of patients with active ulcerative colitis. J Gastroenterol Hepatol. 2010; 25(Suppl 1):S129–133. [PubMed: 20586854]

49*. Wang H, Zhang S, Yu Q, Yang G, Guo J, Li M, Zeng Z, He Y, Chen B, Chen M. Circulating MicroRNA223 is a New Biomarker for Inflammatory Bowel Disease. Medicine (Baltimore). 2016; 95:e2703. This study reported that measurements of serum miR-223 levels correlated well with CRP and erythrocyte sedimentation rate (ESR) to gauge disease activity in IBD patients. [PubMed: 26844512]

50. Wu F, Guo NJ, Tian H, Marohn M, Gearhart S, Bayless TM, Brant SR, Kwon JH. Peripheral blood microRNAs distinguish active ulcerative colitis and Crohn's disease. Inflamm Bowel Dis. 2011; 17:241–250. [PubMed: 20812331]

51. Yang Y, Ma Y, Shi C, Chen H, Zhang H, Chen N, Zhang P, Wang F, Yang J, Yang J, et al. Overexpression of miR-21 in patients with ulcerative colitis impairs intestinal epithelial barrier function through targeting the Rho GTPase RhoB. Biochem Biophys Res Commun. 2013; 434:746–752. [PubMed: 23583411]

52. Zahm AM, Hand NJ, Tsoucas DM, Le Guen CL, Baldassano RN, Friedman JR. Rectal microRNAs are perturbed in pediatric inflammatory bowel disease of the colon. J Crohns Colitis. 2014; 8:1108–1117. [PubMed: 24613022]

53. Mitchell PS, Parkin RK, Kroh EM, Fritz BR, Wyman SK, Pogosova-Agadjanyan EL, Peterson A, Noteboom J, O'Briant KC, Allen A, et al. Circulating microRNAs as stable blood-based markers for cancer detection. Proc Natl Acad Sci U S A. 2008; 105:10513–10518. [PubMed: 18663219]

54. Ng EK, Chong WW, Jin H, Lam EK, Shin VY, Yu J, Poon TC, Ng SS, Sung JJ. Differential expression of microRNAs in plasma of colorectal cancer patients: A potential marker for colorectal cancer screening. Gut. 2009

55. Duttagupta R, DiRienzo S, Jiang R, Bowers J, Gollub J, Kao J, Kearney K, Rudolph D, Dawany NB, Showe MK, et al. Genome-wide maps of circulating miRNA biomarkers for ulcerative colitis. PLoS One. 2012; 7:e31241. [PubMed: 22359580]

56. Zahm AM, Thayu M, Hand NJ, Horner A, Leonard MB, Friedman JR. Circulating microRNA is a biomarker of pediatric Crohn disease. J Pediatr Gastroenterol Nutr. 2011; 53:26–33. [PubMed: 21546856]

57. Iborra M, Bernuzzi F, Correale C, Vetrano S, Fiorino G, Beltran B, Marabita F, Locati M, Spinelli A, Nos P, et al. Identification of serum and tissue micro-RNA expression profiles in different stages of inflammatory bowel disease. Clin Exp Immunol. 2013; 173:250–258. [PubMed: 23607522]

58. Fujioka S, Nakamichi I, Esaki M, Asano K, Matsumoto T, Kitazono T. Serum microRNA levels in patients with Crohn's disease during induction therapy by infliximab. J Gastroenterol Hepatol. 2014; 29:1207–1214. [PubMed: 24447044]

59. Lu C, Chen J, Xu HG, Zhou X, He Q, Li YL, Jiang G, Shan Y, Xue B, Zhao RX, et al. MIR106B and MIR93 prevent removal of bacteria from epithelial cells by disrupting ATG16L1-mediated autophagy. Gastroenterology. 2014; 146:188–199. [PubMed: 24036151]

60. Nguyen HT, Dalmasso G, Muller S, Carriere J, Seibold F, Darfeuille-Michaud A. Crohn's disease-associated adherent invasive Escherichia coli modulate levels of microRNAs in intestinal epithelial cells to reduce autophagy. Gastroenterology. 2014; 146:508–519. [PubMed: 24148619]

61. Palomino-Morales RJ, Oliver J, Gomez-Garcia M, Lopez-Nevot MA, Rodrigo L, Nieto A, Alizadeh BZ, Martin J. Association of ATG16L1 and IRGM genes polymorphisms with inflammatory bowel disease: a meta-analysis approach. Genes Immun. 2009; 10:356–364. [PubMed: 19491842]

62. Zhai Z, Wu F, Chuang AY, Kwon JH. miR-106b fine tunes ATG16L1 expression and autophagic activity in intestinal epithelial HCT116 cells. Inflamm Bowel Dis. 2013; 19:2295–2301. [PubMed: 23899543]

63. Zhai Z, Wu F, Dong F, Chuang AY, Messer JS, Boone DL, Kwon JH. Human autophagy gene ATG16L1 is post-transcriptionally regulated by MIR142-3p. Autophagy. 2014; 10:468–479. [PubMed: 24401604]

64. Brain O, Owens BM, Pichulik T, Allan P, Khatamzas E, Leslie A, Steevels T, Sharma S, Mayer A, Catuneanu AM, et al. The intracellular sensor NOD2 induces microRNA-29 expression in human dendritic cells to limit IL-23 release. Immunity. 2013; 39:521–536. [PubMed: 24054330]

65. Chuang AY, Chuang JC, Zhai Z, Wu F, Kwon JH. NOD2 expression is regulated by microRNAs in colonic epithelial HCT116 cells. Inflamm Bowel Dis. 2014; 20:126–135. [PubMed: 24297055]

66. Li Z, Wu F, Brant SR, Kwon JH. IL-23 receptor regulation by Let-7f in human CD4+ memory T cells. J Immunol. 2011; 186:6182–6190. [PubMed: 21508257]

67. Ma F, Xu S, Liu X, Zhang Q, Xu X, Liu M, Hua M, Li N, Yao H, Cao X. The microRNA miR-29 controls innate and adaptive immune responses to intracellular bacterial infection by targeting interferon-gamma. Nat Immunol. 2011; 12:861–869. [PubMed: 21785411]

68. Pathak S, Grillo AR, Scarpa M, Brun P, D'Inca R, Nai L, Banerjee A, Cavallo D, Barzon L, Palu G, et al. MiR-155 modulates the inflammatory phenotype of intestinal myofibroblasts by targeting SOCS1 in ulcerative colitis. Exp Mol Med. 2015; 47:e164. [PubMed: 25998827]

69. Rossato M, Curtale G, Tamassia N, Castellucci M, Mori L, Gasperini S, Mariotti B, De Luca M, Mirolo M, Cassatella MA, et al. IL-10-induced microRNA-187 negatively regulates TNF-alpha, IL-6, and IL-12p40 production in TLR4-stimulated monocytes. Proc Natl Acad Sci U S A. 2012; 109:E3101–3110. [PubMed: 23071313]

70. Sharma A, Kumar M, Aich J, Hariharan M, Brahmachari SK, Agrawal A, Ghosh B. Posttranscriptional regulation of interleukin-10 expression by hsa-miR-106a. Proc Natl Acad Sci U S A. 2009; 106:5761–5766. [PubMed: 19307576]

71. Tang Y, Luo X, Cui H, Ni X, Yuan M, Guo Y, Huang X, Zhou H, de Vries N, Tak PP, et al. MicroRNA-146A contributes to abnormal activation of the type I interferon pathway in human lupus by targeting the key signaling proteins. Arthritis Rheum. 2009; 60:1065–1075. [PubMed: 19333922]

72. Tekirdag KA, Korkmaz G, Ozturk DG, Agami R, Gozuacik D. MIR181A regulates starvation- and rapamycin-induced autophagy through targeting of ATG5. Autophagy. 2013; 9:374–385. [PubMed: 23322078]

73*. Venza I, Visalli M, Beninati C, Benfatto S, Teti D, Venza M. IL-10Ralpha expression is post-transcriptionally regulated by miR-15a, miR-185, and miR-211 in melanoma. BMC Med Genomics. 2015; 8:81. This study identifies miRNAs involved in regulating IL-10R alpha expression, an area of increased interest given the association of very early onset IBD (VEO-IBD) with mutations in IL-10 signaling. [PubMed: 26631117]

74. Wang P, Hou J, Lin L, Wang C, Liu X, Li D, Ma F, Wang Z, Cao X. Inducible microRNA-155 feedback promotes type I IFN signaling in antiviral innate immunity by targeting suppressor of cytokine signaling 1. J Immunol. 2010; 185:6226–6233. [PubMed: 20937844]

75. Wu W, He C, Liu C, Cao AT, Xue X, Evans-Marin HL, Sun M, Fang L, Yao S, Pinchuk IV, et al. miR-10a inhibits dendritic cell activation and Th1/Th17 cell immune responses in IBD. Gut. 2015; 64:1755–1764. [PubMed: 25281418]

76. Yao R, Ma YL, Liang W, Li HH, Ma ZJ, Yu X, Liao YH. MicroRNA-155 modulates Treg and Th17 cells differentiation and Th17 cell function by targeting SOCS1. PLoS One. 2012; 7:e46082. [PubMed: 23091595]

77. Hebuterne X, Lemann M, Bouhnik Y, Dewit O, Dupas JL, Mross M, D'Haens G, Mitchev K, Ernault E, Vermeire S, et al. Endoscopic improvement of mucosal lesions in patients with moderate to severe ileocolonic Crohn's disease following treatment with certolizumab pegol. Gut. 2013; 62:201–208. [PubMed: 22525883]

78. Rutgeerts P, Sandborn WJ, Feagan BG, Reinisch W, Olson A, Johanns J, Travers S, Rachmilewitz D, Hanauer SB, Lichtenstein GR, et al. Infliximab for induction and maintenance therapy for ulcerative colitis. N Engl J Med. 2005; 353:2462–2476. [PubMed: 16339095]

79. Sandborn WJ, Feagan BG, Rutgeerts P, Hanauer S, Colombel JF, Sands BE, Lukas M, Fedorak RN, Lee S, Bressler B, et al. Vedolizumab as induction and maintenance therapy for Crohn's disease. N Engl J Med. 2013; 369:711–721. [PubMed: 23964933]

80. Sandborn WJ, Gasink C, Gao LL, Blank MA, Johanns J, Guzzo C, Sands BE, Hanauer SB, Targan S, Rutgeerts P, et al. Ustekinumab induction and maintenance therapy in refractory Crohn's disease. N Engl J Med. 2012; 367:1519–1528. [PubMed: 23075178]

81. Sandborn WJ, Rutgeerts P, Enns R, Hanauer SB, Colombel JF, Panaccione R, D'Haens G, Li J, Rosenfeld MR, Kent JD, et al. Adalimumab induction therapy for Crohn disease previously treated with infliximab: a randomized trial. Ann Intern Med. 2007; 146:829–838. [PubMed: 17470824]

82. Sandborn WJ, Colombel JF, Enns R, Feagan BG, Hanauer SB, Lawrance IC, Panaccione R, Sanders M, Schreiber S, Targan S, et al. Natalizumab induction and maintenance therapy for Crohn's disease. N Engl J Med. 2005; 353:1912–1925. [PubMed: 16267322]

83. Dignass A, Van Assche G, Lindsay JO, Lemann M, Soderholm J, Colombel JF, Danese S, D'Hoore A, Gassull M, Gomollon F, et al. The second European evidence-based Consensus on the diagnosis and management of Crohn's disease: Current management. J Crohns Colitis. 2010; 4:28–62. [PubMed: 21122489]

84. Bader AG. miR-34 - a microRNA replacement therapy is headed to the clinic. Front Genet. 2012; 3:120. [PubMed: 22783274]

85. Craig VJ, Tzankov A, Flori M, Schmid CA, Bader AG, Muller A. Systemic microRNA-34a delivery induces apoptosis and abrogates growth of diffuse large B-cell lymphoma in vivo. Leukemia. 2012; 26:2421–2424. [PubMed: 22522790]

86. Janssen HL, Kauppinen S, Hodges MR. HCV infection and miravirsen. N Engl J Med. 2013; 369:878. [PubMed: 23984739]

87. Janssen HL, Reesink HW, Lawitz EJ, Zeuzem S, Rodriguez-Torres M, Patel K, van der Meer AJ, Patick AK, Chen A, Zhou Y, et al. Treatment of HCV infection by targeting microRNA. N Engl J Med. 2013; 368:1685–1694. [PubMed: 23534542]

88. Montgomery RL, Hullinger TG, Semus HM, Dickinson BA, Seto AG, Lynch JM, Stack C, Latimer PA, Olson EN, van Rooij E. Therapeutic inhibition of miR-208a improves cardiac function and survival during heart failure. Circulation. 2011; 124:1537–1547. [PubMed: 21900086]

89. van Rooij E, Sutherland LB, Qi X, Richardson JA, Hill J, Olson EN. Control of stress-dependent cardiac growth and gene expression by a microRNA. Science. 2007; 316:575–579. [PubMed: 17379774]

90. Huang Z, Shi T, Zhou Q, Shi S, Zhao R, Shi H, Dong L, Zhang C, Zeng K, Chen J, et al. miR-141 Regulates colonic leukocytic trafficking by targeting CXCL12beta during murine colitis and human Crohn's disease. Gut. 2014; 63:1247–1257. [PubMed: 24000293]

91. Nata T, Fujiya M, Ueno N, Moriichi K, Konishi H, Tanabe H, Ohtake T, Ikuta K, Kohgo Y. MicroRNA-146b improves intestinal injury in mouse colitis by activating nuclear factor-kappaB and improving epithelial barrier function. J Gene Med. 2013; 15:249–260. [PubMed: 23813877]

Key points

- MiRNAs are a class of small noncoding RNA that regulate gene expression while influencing many biological processes.
- Aberrant expression of miRNAs has been associated with many diseases including IBD.
- MiRNAs are promising as biomarkers and/or therapeutic targets in the management of IBD.

Table 1

miRNAs with altered expression in Crohn's disease

miRNA	Tissue/Body Fluid Type	Expression	Citation
miR-16	Intestinal biopsy, peripheral blood/serum	Elevated	Paraskevi et al.[28], Wu et al. [27]
miR-19b	Intestinal biopsy, peripheral blood/serum	Reduced	Cheng et al. [29], Lewis et al. [30]
miR-21	Intestinal biopsy	Elevated	Fasseu et al. [31], Polytarchou et al. [32], Wu et al. [27], Zahm et al. [33]
miR-23a	Peripheral blood/serum	Elevated	Paraskevi et al.[28]
miR-26a	Saliva	Elevated	Schaefer et al.[34]
miR-29a	Peripheral blood/serum	Elevated	Paraskevi et al.[28]
miR-31	Intestinal biopsy	Elevated	Fasseu et al. [31], Lin et al.[35], Peck et al.[36], Schaefer et al. [34]
miR-101	Intestinal biopsy, peripheral blood/serum, saliva	Elevated	Schaefer et al.[34]
miR-106a	Intestinal biopsy, peripheral blood/serum	Elevated	Fasseu et al. [31], Paraskevi et al.[28], Wu et al. [27]
miR-107	Peripheral blood/serum	Elevated	Paraskevi et al.[28]
miR-126	Peripheral blood/serum	Elevated	Paraskevi et al.[28]
miR-146a	Intestinal biopsy	Elevated	Béres et al. [37], Polytarchou et al. [32], Schaefer et al.[34]
miR-148a	Intestinal biopsy	Elevated	Cheng et al.[29]
miR-155	Intestinal biopsy	Elevated	Béres et al. [37]
miR-191	Peripheral blood/serum	Elevated	Paraskevi et al.[28]
miR-192	Peripheral blood/serum	Elevated	Zahm et al. [33]
miR-196	Intestinal biopsy	Elevated	Brest et al.[38]
miR-199a-5p	Peripheral blood/serum	Elevated	Paraskevi et al.[28], Wu et al.[39]
miR-200c	Peripheral blood/serum	Elevated	Paraskevi et al.[28]
miR-203	Intestinal biopsy	Reduced	Peck et al.[36]
miR-215	Intestinal biopsy	Elevated	Peck et al.[36]
miR-223-3p	Intestinal biopsy, peripheral blood/serum	Elevated	Peck et al.[36], Wang et al.[40], Wu et al. [27]
miR-301a	Intestinal biopsy, peripheral blood/serum	Elevated	He et al.[41]
miR-320a	Intestinal biopsy	Reduced	Pierdomenico et al.[42]
miR-320b	Intestinal biopsy	Reduced	Pierdomenico et al.[42]
miR-320c	Intestinal biopsy	Reduced	Pierdomenico et al.[42]
miR-375	Intestinal biopsy	Reduced	Schaefer et al.[34], Zahm et al. [33]
miR-362-3p	Peripheral blood/serum	Elevated	Paraskevi et al.[28], Wu et al.[39]
miR-532-3p	Peripheral blood/serum	Elevated	Paraskevi et al.[28], Wu et al.[39]

Table 2

miRNAs with altered expression in ulcerative colitis

miRNA	Tissue/Body Fluid Type	Expression	Citation
let-7i	Intestinal biopsy	Elevated	Zahm et al. [33]
miR-19a	Intestinal biopsy	Elevated	Schaefer et al.[34]
miR-20b	Intestinal biopsy	Elevated	Coskun et al.[43]
miR-21	Intestinal biopsy, peripheral blood/ serum, saliva	Elevated	Feng et al. [44], Paraskevi et al.[28], Polytarchou et al. [32], Schaefer et al.[34], Takagi et al. [45], Yang et al.[46], Wu et al.[26], Zahm et al. [33]
miR-23a-3p	Peripheral blood/serum	Elevated	Polytarchou et al. [47]
miR-24	Intestinal biopsy	Elevated	Zahm et al. [33]
miR-26	Intestinal biopsy	Reduced	Koukos et al. [48]
miR-28-5p	Peripheral blood/serum	Elevated	Paraskevi et al.[28], Wu et al.[39]
miR-29a	Intestinal biopsy	Elevated	Fasseu et al. [31], Wu et al.[26]
miR-31	Intestinal biopsy, saliva	Elevated	Fasseu et al. [31], Lin et al.[35], Schaefer et al.[34]
miR-101	Intestinal biopsy	Reduced	Koukos et al. [48]
miR-101	Intestinal biopsy, peripheral blood/ serum	Elevated	Schaefer et al.[34]
miR-124	Intestinal biopsy (Pediatric only)	Reduced	Koukos et al. [48]
miR-125b	Intestinal biopsy	Elevated	Coskun et al.[43]
miR-126	Intestinal biopsy	Elevated	Fasseu et al. [31], Feng et al.[44]
miR-142-3p	Intestinal biopsy, peripheral blood/ serum, saliva	Elevated	Schaefer et al.[34], Zahm et al. [33]
miR-142-5p	Peripheral blood/serum	Elevated	Schaefer et al.[34]
miR-146a	Intestinal biopsy	Elevated	Béres et al. , Polytarchou et al. [32], Zahm et al. [33]
miR-150	Intestinal biopsy	Elevated	Bian et al. [49]
miR-151-5p	Peripheral blood/serum	Elevated	Paraskevi et al.[28], Wu et al.[39]
miR-155	Intestinal biopsy, peripheral blood/ serum	Elevated	Béres et al. [37], Min et al. [50], Paraskevi et al.[28], Takagi et al. [45]
miR-192	Peripheral blood/serum	Elevated	Zahm et al. [33]
miR-192	Intestinal biopsy	Reduced	Wu et al.[26], Zahm et al. [33]
miR-194	Intestinal biopsy	Reduced	Zahm et al. [33]
miR-199a-5p	Peripheral blood/serum	Elevated	Paraskevi et al.[28], Wu et al.[39]
miR-200b	Intestinal biopsy	Reduced	Zahm et al. [33]
miR-214	Intestinal biopsy	Elevated	Polytarchou et al. [32]
miR-223-3p	Peripheral blood/serum	Elevated	Koukos et al.[51], Polytarchou et al. [47], Schaefer et al.[34], Wang et al.[40]
miR-301a	Intestinal biopsy, peripheral blood/ serum	Elevated	He et al. [41]
miR-320a	Intestinal biopsy	Reduced	Pierdomenico et al.[42]
miR-320b	Intestinal biopsy	Reduced	Pierdomenico et al.[42]
miR-320c	Intestinal biopsy	Reduced	Pierdomenico et al.[42]
miR-320e	Peripheral blood/serum	Elevated	Polytarchou et al. [47]

miRNA	Tissue/Body Fluid Type	Expression	Citation
miR-375	Intestinal biopsy	Reduced	Zahm et al. [33]
miR-375	Peripheral blood/serum	Elevated	Schaefer et al.[34]
miR-494	Peripheral blood/serum	Elevated	Schaefer et al.[34]
miR-4284	Intestinal biopsy	Reduced	Koukos et al.[51]
miR-4454	Peripheral blood/serum	Elevated	Polytarchou et al. [47]

Table 3

IBD-associated genes targeted by miRNAs

Gene	miRNA	Citation
ATG5	miR-30c miR181a	Nguyen et al.[59] Tekirdag et al.[63]
ATG16L1	miR-93 miR-106b miR130a miR142-3p	Lu et al.[58] Lu et al.[58]; Zhai et al.[61] Nguyen et al.[59] Zhai et al.[62]
CXCL5	miR-4284	Koukos et al.[51]
IFNG (IFNγ)	miR-29a, 29b, and 29c	Ma et al.[64]
IKBA (IκBα)	miR-126	Feng et al.[44]
IL10	miR-106a	Sharma et al.[65]
IL10RA (IL10Rα)	miR-15a miR-185 miR-211	Venza et al.[66] Venza et al.[66] Venza et al.[66]
IL12B (IL12p40)	miR-29a, 29b, and 29c miR-10a	Brain et al.[67] Wu et al.[68]
IL23R	Let-7f	Li et al.[69]
IRF5	miR-146a	Tang et al.[70]
IRGM	miR-196	Brest et al.[38]
NOD2	miR-10a miR-192 miR-320a, 320b, and 320c	Wu et al.[68] Chuang et al.[71] Pierdomenico et al.[42]
SOCS1	miR-155	Pathak et al.[72]; Wang et al.[73]; Yao et al. [74]
STAT3	miR-124	Koukos et al.[48]
TNFA (TNFα)	miR-187	Rossato et al.[75]