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Circulating MicroRNAs as Biomarkers for Inflammatory Diseases

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Abstract

MicroRNAs (miRNAs), a class of small, non-coding RNA molecules with gene regulatory functions, have emerged to play a critical role in the pathogenesis of a variety of diseases. Current technological advances allow accurate, high throughput profiling of miRNA abundance in different tissues. More recently, extracellular, circulating miRNAs have begun to be demonstrated as highly stable, blood-based biomarkers for diseases. Understanding the interactions between circulating miRNAs and clinical phenotypes can enhance our knowledge of complex diseases and traits. On the other hand, given the advantages of utilizing blood-based biomarkers (e.g., convenience in collecting samples), circulating miRNAs as biomarkers may improve both disease diagnosis and management. Particularly, we reviewed recent progress in identifying circulating miRNAs as biomarkers for several common inflammatory diseases including asthma, inflammatory bowel disease, and rheumatoid arthritis. Current studies showed a promising future of using circulating miRNAs in the care of inflammatory diseases.

Keywords

Asthma; biomarkers; circulating markers; inflammatory bowl disease; microRNA; rheumatoid arthritis

MICRORNAS

MicroRNAs (miRNAs) are endogenous single-strand, non-coding RNAs of 18–25 nucleotides in length, that post-transcriptionally regulate gene expression through sequence-specific interaction with target messenger RNAs (mRNAs). MiRNAs primarily bind to the 3′ untranslated regions (UTR) of mRNAs to inhibit protein translation or cause mRNA

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CONFLICTS OF INTEREST

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degradation [1–4]. Since the discovery of *lin-4*, the first miRNA molecule in *Caenorhabditis elegans* in 1993, increasing number of miRNAs have been identified in a wide variety of species including humans [5–7]. Currently, there are 2,042 mature human miRNAs listed in the miRBase MicroRNA Registry (http://www.mirbase.org, release 19). The sequences of miRNAs are evolutionary conserved across species, suggesting the importance of miRNAs functions [8]. There has been extensive evidence indicating that miRNAs exhibit critical regulatory roles in many biological processes, such as development, differentiation, cell proliferation, and apoptosis [8]. Thus, aberrant expression of miRNAs has been related to various human diseases including cancers, inflammation conditions, cardiovascular diseases and neurological disorders [9–12].

MiRNAs are primarily transcribed in nucleus and undergo sequential processing by RNase III enzymes Drosha and Dicer. Then one strand of mature miRNA is unwound from a double-stranded miRNA to incorporate into the RNA-induced silencing complex (RISC) and perform its function in cytosol [13, 14]. RISC is the protein complex responsible for the gene silencing, which is mainly composed of Argonaute (AGO) protein as catalytic component [15]. The mutations occurred in miRNA genes may lead to an incorrect processing of the miRNAs, thus altering miRNA expression levels. Genetic studies have shown associations among single nucleotide polymorphisms (SNPs), miRNA expression, gene expression, and human disease phenotypes [16].

The expression of many miRNAs is in a tissue- or developmental stage-specific manner and the altered miRNA profiles may reflect the abnormality in developmental regulation or related tissue function. Identifying these differentially expressed key miRNAs hold promise as diagnostic markers or therapeutic targets in diseases [17–20].

CIRCULATING MIRNA

A unique characteristic of miRNAs is that their short sequences are exceptionally stable compared with mRNAs [21]. Recently, intact, cell-free miRNAs have been detected in serum and plasma samples, and are resistant to nuclease digestion. These miRNAs are preserved in circulation and are quantifiable, which support their potential roles as non-invasive, sensitive diagnostic or progression biomarkers in various diseases [22–24]. Besides in serum and plasma, extracellular miRNAs are also found in other body fluids, such as urine and saliva [25, 26]. In this review, we will mainly focus on miRNAs circulated in blood.

One of the first studies measuring cell-free miRNA levels in serum was published by Lawrie *et al.*, in early 2008 [23]. In this study, patients with diffuse large B cell lymphoma were found to have a longer relapse-free survival when high serum levels of miR-21 were detected. Thereafter, the isolation of circulating miRNAs in serum or plasma was reported in many other studies [22, 24]. Notably, these circulating miRNAs were not unique in humans. They are also found in the serum of mice, rats, calves and horses [22]. To date, although the existence of circulating miRNAs has been determined and shown conservation in mammalian species, the origin of the miRNAs and the mechanisms by which miRNAs are released in the bloodstream remain unclear.

Accumulating evidence has shown that the existence of circulating miRNAs are not naked but in different packaging modes. Serum or plasma contains ribonuclease, which suggests that extracellular miRNAs are protected against RNase digestion. Recent studies have revealed that cell-free miRNAs are contained in two types of small membrane vesicles called exosomes and microvesicles. Microvesicles are 50–1000 nm lipid vesicles shed from cell membrane [27], while exosomes are 30–100 nm particles released from the cell when multivesicular bodies fuse with the plasma membrane [28]. Valida *et al.*, found several selective packaging of exosomal miRNAs [29]. Hunter *et al.*, detected miRNAs in purified human peripheral blood microvesicles [30]. These studies reinforced that extracellular miRNAs are protected by membrane vesicles. Meanwhile, a study of cells from glioblastoma indicated that miR-21 could be found at 40-fold elevated levels in the exosomes isolated from patient sera compared to controls [31]. Mittelbrunn *et al.*, observed that exosomes of T, B and dendritic immune cells contain miRNA signatures that differ from those of their parent cells [32]. More and more evidence demonstrated that miRNA patterns in exosomes or microvesicles were disease-related and could be used in diagnosis or prognosis prediction. Additionally, miRNAs are found to be packaged into apoptotic bodies or high density lipoprotein (HDL) particles [33, 34]. Interestingly, other studies reported that circulating miRNAs could be vesicle independent and protected by proteins of Argonaute (AGO) family [35] in nuclease-rich bloodstream.

As mentioned before, besides the complicated packaging modes of circulating miRNAs, the release mechanisms of these miRNAs have not yet elucidated. One of the potential mechanisms is that passive release occurs during cell death or disruption of plasma membrane integrity, which is supported by the detection of heart specific miR-208 in serum after heart tissue injury [36]. Other studies proposed that miRNAs were released through ceramide-dependent secretory machinery and performed regulatory function after transferring to recipient cells by exosomes or microvesicles [37]. Current researches suggest that both hypotheses might be true; however, additional evidence is needed.

The role of circulating miRNA

The levels of specific, circulating miRNAs in blood have been shown to be associated with various pathological conditions, which make extracellular miRNAs promising non-invasive biomarkers for certain human diseases, especially in cancers. In case of disease diagnostics, as mentioned above, Lawrie *et al.*, were the first to discover that tumor specific deregulation of miR-21 is highly frequent in the serum of diffuse large B-cell lymphoma patients [23]. Compared to those of healthy individuals, Mitchell *et al.*, found that circulating miR-141 was significantly elevated in serum of metastatic prostate cancer [24]. For early tumor diagnosis in pancreatic cancer, analyzing a panel of four miRNAs in plasma: miR-21, miR-155, miR-196b and miR-210, can distinguish pancreatic adenocarcinoma patients from healthy controls with a sensitivity of 64% and a specificity of 89% [38]. Furthermore, circulating miRNAs can be used to monitor tumor recurrence. For example, Yamamoto *et al.*, demonstrated that the serum levels of miR-500 were elevated in hepatocellular carcinoma (HCC) patients, and the level of this circulating miRNA reduced significantly after surgery [39]. Therefore, the authors proposed to monitor the recurrence of HCC by measuring miR-500 as a blood-based biomarker. Moreover, a combination of a few serum

miRNA expression signatures was found to predict clinical outcomes in non-small-cell lung cancer (NSCLC). Particularly, NSCLC patients with higher levels of miR-486 and miR-30d and lower levels of miR-1 and miR-499 had significantly short survival, which suggest these miRNAs can be valuable as prognostic markers [40].

Circulating miRNA quantification

Circulating miRNAs can be profiled by three major platforms: PCR, microarray and sequencing. Quantitative real-time PCR (qRT-PCR) is one of the most commonly used methods for the quantification of miRNAs in the circulation. For example, Wang G *et al.*, determined serum and urinary supernatant levels of miR-146a, miR-155, miR-205, miR-192 and miR-200 family by qRT-PCR in 40 patients with systemic lupus erythematosus (SLE) and 30 healthy controls [41, 42]. The qRT-PCR method is also often employed to validate the expression of miRNAs after detection of a distinct profile by microarray. More recently, technical advancement in PCR arrays (*e.g.*, serum & plasma miRNA PCR Array; http://www.sabiosciences.com/mirna_pcr_product/HTML/MIHS-106Z.html) made it possible to simultaneously measure the majority of circulating miRNAs all at once [43, 44]. Microarray is another tool to measure the circulating miRNAs, which has much higher throughput compared to qPCR. In the study of Duttagupta *et al.*, genome-wide circulating miRNAs in microvesicles, peripheral blood mononuclear cells (PBMCs) and platelets have been mapped with Affymetrix Genechip miRNA array from a cohort of 20 ulcerative colitis (UC) patients and 20 normal individuals [45]. Microfluidics-based measurement is a new high throughput "digital PCR" technology to quantify trace molecules, which can significantly decrease the amount of starting molecules required by microarray [46]. Zahm *et al.*, initially explored serum miRNA levels using a microfluidic qPCR array platform, and subsequently validated the findings in larger sample sets with pediatric Crohn's disease (CD) [47]. Recently, massively parallel sequencing technology has been increasingly utilized to identify novel miRNAs and to analyze miRNA expression levels. Chen *et al.*, employed Solexa sequencing platform to identify specific expression patterns of serum miRNAs for lung cancer, colorectal cancer, and diabetes [22]. Two other studies were carried out with the SOLiD sequencing platform. For example, Semenov *et al.*, investigated the components of non-coding RNAs in plasma samples of healthy individuals [48]. Bellingham *et al.*, showed that exosomes released by prion-infected neuronal cells contained increased let-7b, let-7i, miR-128a, miR-21, miR-222, miR-29b, miR-342-3p and miR-424 levels with decreased miR-146a levels compared to non-infected exosomes [49]. Given the diversity in the quantification methods, research findings on circulating miRNAs may and is often conflicting. Therefore, it is extremely important to understand the methods used from each study to properly interpret and compare the results from different studies.

MIRNA AND CIRCULATING MIRNA IN INFLAMMATORY DISEASES

Recent evidence has shown that specific miRNAs are involved in regulating immune response and immune cell development, which are crucial to the pathogenesis of a variety of inflammatory diseases. For instances, miR-155 affected antigen presentation and miR-181a regulated T-cell receptor signaling in the adaptive immune response [50] while miR-146a played pivotal roles in the innate immune response [51]. The expression of miR-150 is

important to the development of mature T- and B-cells. Over-expression of miR-150 in hematopoietic stem cells had little effect on the formation of T-cells, but greatly impaired the formation of mature B-cells [52]. One source of circulating miRNAs in the patients of inflammatory diseases is probably from the activated immune cells. However, the tissue damage caused by the immune attack may also contribute to the production of miRNAs in the sera of patients.

Indeed, recent research findings suggest the role of circulating miRNA in various inflammatory diseases. For example, 72 miRNAs were examined in 12 controls and 20 chronic obstructive pulmonary disease (COPD) patients, a disease characterized by lower airway inflammation. Serum levels of miR-20a, miR-28-3p, miR-34c-5p, and miR-100 were found to be significantly down-regulated, while serum miR-7 was up-regulated when comparing to the controls [53]. Another investigation was performed in patients with active pulmonary tuberculosis (TB). Up-regulated circulating miR-29a distinguished TB patients from healthy controls with a sensitivity of 83% and a specificity of 80%, which suggest a great potential of extracellular miR-29a as a marker for the TB detection [54]. In mouse models of liver damage and inflammation, circulating miR-155, a regulator of inflammation, was increased in serum/plasma in alcoholic and inflammatory liver injury [55]. In this review, recent progress in identifying circulating miRNAs as biomarkers for several common inflammatory diseases including asthma, inflammatory bowel disease, and rheumatoid arthritis will be summarized in more details.

CIRCULATING MIRNA AND INFLAMMATORY BOWEL DISEASE

Inflammatory bowel disease (IBD) is a group of inflammatory conditions of the colon and small intestines. The etiology was believed to base on host genetics, immune response, and environmental factors [56]. Two major types of IBD are Crohn's disease (CD) and ulcerative colitis (UC). These two similar diseases can be distinguished through clinical and pathological evaluation and by gene expression studies [57]. Given the important role of miRNAs in gene expression regulation, these small non-coding RNAs have been extensively evaluated for their role in IBD diagnosis. Furthermore, latest genome-wide association studies also supported the role of miRNAs in the development of IBD, since the onset of IBD can be linked to genetic polymorphisms in regulatory miRNAs [58].

To date, over 100 miRNAs have been indicated to be differentially expressed in IBD when compared to healthy normal controls [56]. Methods to quantify miRNAs include quantitative PCR and microarrays as well as *in situ* hybridization. The numbers of miRNAs evaluated range from a single miRNA to all miRNAs in the human genome. To evaluate the differential miRNA expression in different forms of IBD and at different stages, tissue samples from various sections of digestive track have been collected through colonoscopy and compared. The differential expression of certain miRNAs has been confirmed by various studies. For example, increased miR-106a expression was observed in colon tissues, serum and peripheral blood samples from CD patients when compared to healthy controls [47, 59–61]. Several miRNAs have been shown to be differentially expressed in both UC and CD, which may suggest their role in general inflammatory processes. For example, increased expression of miR-126 was found in active UC and CD patients in both colon and

peripheral blood samples [59, 60, 62]. miR-126* [59], miR-127-3p [59], miR-29a [59, 60, 62], miR-29b [59], miR-324-3p [45, 59] expression increased in both active and inactive forms of UC and CD. Increased expression of miR-16 was seen in colon, terminal ileum, serum and peripheral blood samples from both UC and CD patients [47, 60–62]. The expression of another miRNA, miR-21, was found to be up-regulated in various tissues from both UC and CD patients when compared to normal controls [47, 59–63]. Other miRNAs are distinguishing only one disease from the healthy controls, such as the up-regulation of miR-133b [59], miR-146a [59], miR-149* [64], miR-185 [47, 59], miR-191 [60, 61], miR-29c [59], miR-30b [59], miR-34c-5p [59] in CD. Decreased expression of miR-215 [59], miR-320a [59], miR-346 [59] was observed in the colon tissues from active and inactive UC patients.

Circulating miRNA and IBD

The gold standard for the diagnosis and evaluation of IBD is endoscopy/colonoscopy, although it is invasive, costly, and associated with risks to the patient. Therefore, circulating miRNAs have emerged as promising noninvasive biomarkers [47] for IBD. A summary of potential circulating miRNAs for IBD can be found in Table 1.

Increased expression of miR-151-5p, miR-28-5p was observed by two independent studies of circulating miRNA markers in peripheral blood samples from active UC patients [60, 64]. Wu *et al.*, identified higher miR-199a-5p expression in the peripheral blood obtained from both UC and CD patients [64]. The increased expression of this circulating miRNA marker in both diseases was confirmed by Paraskevi *et al.*, in a larger study of 128 CD, 88 UC and 162 healthy controls [60]. Wu *et al.*, also identified and validated the increased expression of miR-340*, miR-362-3p, miR-532-3p and miRPlus-E1271 in peripheral blood samples from both UC and CD patients and demonstrated and validated the decreased expression of miR-505* in UC patients peripheral blood [64].

Some studies explored the relationships between altered miRNA expression in circulation and those at the disease tissues. Sometimes, the direction of the miRNA expression change in the disease tissue is shown to be different from that observed in the peripheral district where the expression levels of circulating miRNAs were quantified. For example, decreased expression of miR-188-5p was observed in colon tissues from both active and inactive UC patients when compared to healthy controls [59]; however, in platelets derived from active UC patients, miR-188-5p expression is higher compared to those of healthy controls [45]. Decreased miR-19b expression was observed in CD patients' sigmoid colon mucosa [61]; while separate study of serum from 46 pediatric CD patients showed increased expression of this miRNA when compared to 32 healthy age-matched controls [47]. Interestingly, the increased expression of miR-19a was observed in both colon and serum of CD patients when compared to controls [47, 59].

CIRCULATING MIRNA AND RHEUMATOID ARTHRITIS

In rheumatoid arthritis (RA), miRNA expression can be evaluated in several different tissues including but not limited to fibroblast-like synoviocytes (FLS), synovium fluid, rheumatoid arthritis synovial fibroblast (RASFs), articular cartilage, as well as in circulation (*e.g.*,

PBMC, PBL). miRNAs were evaluated as potential markers to distinguish people with or without RA and they were also evaluated to distinguish patients with RA or osteoarthritis (OA). Therefore, the differential expression for miRNAs is often compared between these two different types of diseases.

In this disease category, there are relatively smaller numbers of differential expression of miRNA that are known to date (less than 20) [65]. Among them, miR-124a [66, 67], miR-19a [68], miR-23b [69], miR-34a* [70] were found decreased in RA; while miR-146a [71–73], miR-155 [71, 73, 74], miR-16 [71], miR-203 [73], miR-223 [71, 75, 76] increased in RA when compared to OA.

Circulating miRNA and RA

A summary of all potential circulating miRNA biomarkers for RA to date can be found in Table 1. Specifically, the increased expression of miR-146a in RA was not only seen in synovial tissues and fibroblasts [71–73], but also in RA patients' plasma, PBMCs, and CD4+ T cells [71, 77–80] as compared to normal controls. Furthermore, the same increased expression was also observed for miR-16 [71, 77, 80, 81] and miR-223 [81, 82] in both RA disease tissue and in their PBMCs, plasma and/or T-lymphocytes.

Notably, conflict findings were observed for miR-132 with increased miR-132 expression was found in PBMCs derived from RA patients when compared to those of healthy controls [80]; while in the plasma samples obtained from both RA and OA patients, miR-132 expression was lower than that in healthy controls [71].

CIRCULATING MIRNA AND ASTHMA

Asthma is a common chronic inflammatory airway disorder that is characterized by variable and recurring airflow obstruction, chronic airway inflammation and bronchial hyper-responsiveness [83]. To study the role of miRNA in asthmatic pathogenesis, both human and mice models have been employed. Specifically, bronchial epithelial cells, lung tissues, and T cells have been evaluated. To date, over 100 miRNAs have been found to have differential expression in asthmatic patients when compared to healthy normal controls [83]. However, unlike what was seen in IBD and RA, the direction of observed differentially expressed miRNA in asthma are often conflicting from study to study [84, 85]. This could be due to the tissue studied, the timing of sampling or the small study sample size. The only exception is miR-221, which was found to be up-regulated when comparing 16 asthmatics to 12 healthy controls [86]. Qin *et al.*, found blocking miR-221 resulted in a reduction of airway inflammation in the OVA-induced murine asthma model, supporting the role of miR-221 in asthma [87].

Circulating miRNA and asthma

To our knowledge, there has not been reported circulating miRNA biomarker for asthma. Most of the studies on miRNAs in blood for asthma risk have been focusing on T cells. In addition, as it is in the field of studying relationship between miRNA and asthma risk, conflicting results were also seen in relationship between blood cell miRNA and asthma. For example, increased miR-155 expression in bronchial epithelial cells was seen when

comparing 7 asthma patients to 7 healthy donors [84]; while decreased miR-155 expression was observed in CD4+ T cells from asthmatic patients and further decrease was seen when disease progress from mild to severe asthma [88].

ISSUES ASSOCIATED TO USING CIRCULATING MIRNA AS A BIOMARKER

Although promising, there are a number of issues associated with identifying and utilizing circulating miRNAs as biomarkers. 1) Depend on the sources of obtaining samples, the procedure for miRNA isolation may have different yields. In blood, circulating miRNAs can be isolated from serum as well as plasma, but the yield differs. Wang *et al.*, observed higher miRNA concentrations in serum samples compared to the corresponding plasma samples from the same individuals, while a separate group reported lower miRNA yield in the serum samples [89, 90]. 2) The cellular origin of circulating miRNA has not been determined. In healthy individuals, Chen *et al.*, found miRNA profiles of serum extensively overlap with those of blood cells [22]. However, another study reported AGO-specific miRNA profiles in blood cells differed significantly from miRNAs profiles in plasma indicating that most circulating miRNAs is likely to derive from non-blood cells [91]. Interestingly, tissue-specific miRNAs, such as miR-208a in heart, miR-122 in liver, have been detected in plasma consistently, which indicates those tissues contribute to circulating miRNAs. For cancer patients, distinct cancer-specific miRNA signatures have been found in serum or in microvesicles and exosomes released by cancer tissue to circulation [30, 31]. One can speculate each circulating miRNA may represent specific organ miRNA expression or that of only blood. Furthermore, a recent report showed that both blood cell counts and hemolysis condition can alter plasma miRNA levels by up to 50-fold [92]. This discovery emphasized the need to carefully interpreting the findings on circulating miRNA markers. 3) Different miRNA quantification methods might influence results. For qPCR or microarray methods, the differences in RNA isolation protocol, primer design, house keeping control selection, platform selection could all contribute to the differences in the observed circulating miRNA expression. 4) Depend on the time of collecting circulating miRNAs, their expression pattern may change. The timing of collection could refer to different disease states, or time after stimulation (*e.g.*, surgery, drug treatment) [39, 93]. For example, miR-122, miR-181a, miR-15b, let-7e, miR-17, miR-143 were up-regulated from non-neoplastic tissue to dysplasia, but down-regulated from dysplasia to colorectal cancer in Crohn's disease patients [94]. To date, the only study that has profiled the global miRNA expression in PBMCs from the same individual over time was conducted in a 54-year-old male volunteer over 14-month period [95]. Dynamic changes in miRNAs were observed which highlights the need of surveying dynamic change of miRNAs to determine the suitable biomarkers for different pathological and physiological conditions. To our knowledge, this type of longitudinal observation has not been done for circulating miRNAs. Taken together, candidate circulating miRNA biomarkers need to be interpreted at clearly defined conditions and be further validated before rendering to real practice.

CONCLUSION

miRNAs play an important role in inflammatory diseases. The advanced understanding of biology and the maturation in quantification methods allow the development of circulating

miRNAs as biomarkers for disease diagnosis and management. The relatively simple and cheaper sample acquisition, and the low risk to patients made the research of circulating miRNA an attractive field in biomarker study. However, it is critical to understand the conditions under which a circulating miRNA was discovered. Further clinical validation and functional mechanistic studies are needed before circulating miRNAs can be incorporated into clinical practice.

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Table 1

Potential Circulating miRNA Biomarkers in IBD (UC and CD), and RA

Disease	miRNA	Expression in Disease Compared to Healthy Controls	Site of Observaion	Concordant Expression Trend in Disease Tissue	References
active ulcerative colitis (UC)	miR-103-2*	increased	peripheral blood	NA	[66]
	miR-1263	increased	micro-vesicle fractions	NA	[46]
	miR-151-5p	increased	peripheral blood	NA	[66]
		increased	peripheral blood	NA	[60]
	miR-155	increased	peripheral blood	Y	[60]
	miR-16	increased	peripheral blood	Y	[60]
	miR-199a-5p	increased	peripheral blood	NA	[66]
		increased	peripheral blood	NA	[60]
	miR-202	increased	micro-vesicle fractions	NA	[46]
	miR-21	increased	peripheral blood	Y	[60]
	miR-221*	increased	micro-vesicle fractions	NA	[46]
	miR-28-5p	increased	peripheral blood	NA	[66]
		increased	peripheral blood	NA	[60]
	miR-340*	increased	peripheral blood	NA	[66]
	miR-362-3p	increased	peripheral blood	NA	[66]
	miR-455-3p	increased	micro-vesicle fractions	NA	[46]
	miR-505*	decreased	peripheral blood	NA	[66]
	miR-532-3p	increased	peripheral blood	NA	[66]
	miR-603	increased	micro-vesicle fractions	NA	[46]
	miR-628-5p	increased	micro-vesicle fractions	NA	[46]
	miRPlus-E1271	increased	peripheral blood	NA	[66]
inactive ulcerative colitis (UC)	miR-103-2*	increased	peripheral blood	NA	[66]
	miR-362-3p	increased	peripheral blood	NA	[66]
	miR-505*	decreased	peripheral blood	NA	[66]
	miR-532-3p	increased	peripheral blood	NA	[66]
active Crohn's disease (CD)	let-7b	increased	serum	NA	[48]

Disease	miRNA	Expression in Disease Compared to Healthy Controls	Site of Observaion	Concordant Expression Trend in Disease Tissue	References
	let-7g	increased	serum	NA	[48]
	miR-106a	increased	peripheral blood	Y	[60]
	miR-106b	increased	serum	NA	[48]
	miR-107	increased	peripheral blood	NA	[60]
	miR-126	increased	peripheral blood	Y	[60]
	miR-140-5p	increased	serum	NA	[48]
active Crohn's disease (CD)	miR-149*	decreased	peripheral blood	NA	[66]
	miR-16	increased	peripheral blood	Y	[60]
		increased	serum	Y	[48]
	miR-17	increased	serum	NA	[48]
	miR-185	increased	serum	Y	[48]
	miR-191	increased	peripheral blood	Y	[60]
	miR-192	increased	serum	NA	[48]
	miR-195	increased	serum	NA	[48]
	miR-199a-5p	increased	peripheral blood	NA	[60]
		increased	peripheral blood	NA	[66]
	miR-19a	increased	serum	Y	[48]
	miR-19b	increased	serum	N	[48]
	miR-200c	increased	peripheral blood	NA	[60]
	miR-20a	increased	serum	NA	[48]
	miR-20b	increased	serum	NA	[48]
	miR-21	increased	serum	Y	[48]
	miR-23a	increased	peripheral blood	NA	[60]
	miR-25	increased	serum	NA	[48]
	miR-29a	increased	peripheral blood	NA	[60]
	miR-301a	increased	serum	NA	[48]
	miR-30d	increased	serum	NA	[48]
	miR-30e	increased	serum	NA	[48]
	miR-340*	increased	peripheral blood	NA	[66]

Disease	miRNA	Expression in Disease Compared to Healthy Controls	Site of Observaion	Concordant Expression Trend in Disease Tissue	References
	miR-362-3p	increased	peripheral blood	NA	[66]
		increased	peripheral blood	NA	[60]
	miR-451	increased	serum	NA	[48]
	miR-484	increased	serum	NA	[48]
	miR-486-5p	increased	serum	NA	[48]
	miR-532-3p	increased	peripheral blood	NA	[66]
		increased	peripheral blood	NA	[60]
	miR-92a	increased	serum	NA	[48]
	miR-93	increased	serum	NA	[48]
	miRPlus-E1271	increased	peripheral blood	NA	[66]
	miRPlus-F1065	decreased	peripheral blood	NA	[66]
inactive Crohn's disease (CD)	miR-149*	decreased	peripheral blood	NA	[66]
	miR-340*	increased	peripheral blood	NA	[66]
rheumatoid arthritis (RA)	miR-132	decreased (when comparing RA and OA to healthy)	plasma	NA	[73]
	miR-146a	correlate with tender joint counts and 28-joint Disease Activity Score.	plasma	Y	[73]
	miR-16	increased	plasma	Y	[83]
	miR-21	increased	plasma	NA	[83]
	miR-223	increased	plasma	Y	[83]
	miR-451	increased	plasma	NA	[83]

Bolded miRNAs were identified using microarray and replicated using qPCR method.

NA: not available. Y: Yes.