ERURJ **2023**, 2, 4, 699 - 722

(Review)

The Role of MicroRNAs as diagnostic biomarkers in Rheumatoid arthritis

Nada R. Mohamed[1,*], Gamil M. Abd-Allah[1]

[1]*Department of Biochemistry, Faculty of Pharmacy Egyptian Russian University, Cairo 11829, Egypt.*

*Corresponding author: Nada R. Mohamed, E-mail: nada_raafat@eru.edu.eg,

Received 19th June 2023, Revised 5th July 2023, Accepted 27th October 2023

DOI: 10.21608/ERURJ.2023.218067.1042

ABSTRACT

Rheumatoid arthritis (RA) is an autoimmune inflammatory disease. Approximately 1% of the world's population and 0.29% of Egyptians suffer from this disease. It is accompanied by ongoing inflammation and synovium hyperplasia, which, if left untreated, can cause severe joint degeneration and abnormalities. This disease's etiology is still unknown; however, RA development is significantly influenced by several genetic and environmental variables. Even though various treatments are accessible to the clinician, they are prone to failure or limited responses, seldom attain long-term remission, as well as are accompanied by systemic complications. Therefore, recent research on the epigenetics of RA has mainly focused on microRNA (miRNA) dysregulation in the disease, explains various RA pathophysiology features, and reveals new biomarkers for the diagnosis and prognosis of RA. Here, we reviewed the data on the deregulations of miRNA expression in RA that are currently accessible and discussed their potential as diagnostic biomarkers for patients with RA.

Keywords: Rheumatoid arthritis, MicroRNAs, RA diagnosis.

1- Introduction

Rheumatoid arthritis (RA) is a chronic autoimmune disorder that affects the metabolic, vascular, bone, and psychological systems as well as causing gradual articular deterioration ***(1)***. The pathophysiology of RA is characterized by attacking synovial joints which

results in pain, swelling, and deformity with movement limitation ***(2)***. Early treatment can significantly improve patient outcomes and prevent serious disability, although a large proportion of patients continue to struggle with ineffective treatment ***(3)***.

1.1 Epidemiology:

Rheumatoid arthritis is one of the most common autoimmune diseases that is ranked as the 42nd highest disease-causing disability ***(4)***. It affects about 0.1–2.0% of the population worldwide ***(5)***.

Meta–estimates of regional RA prevalence rates in low- and middle-income countries were 0.6% for Europe, 0.4% for Southeast Asia, 0.37% for Eastern Mediterranean, 0.42% for Western Pacific, and 1.2% for America as shown in **(figure 1)** ***(6).***

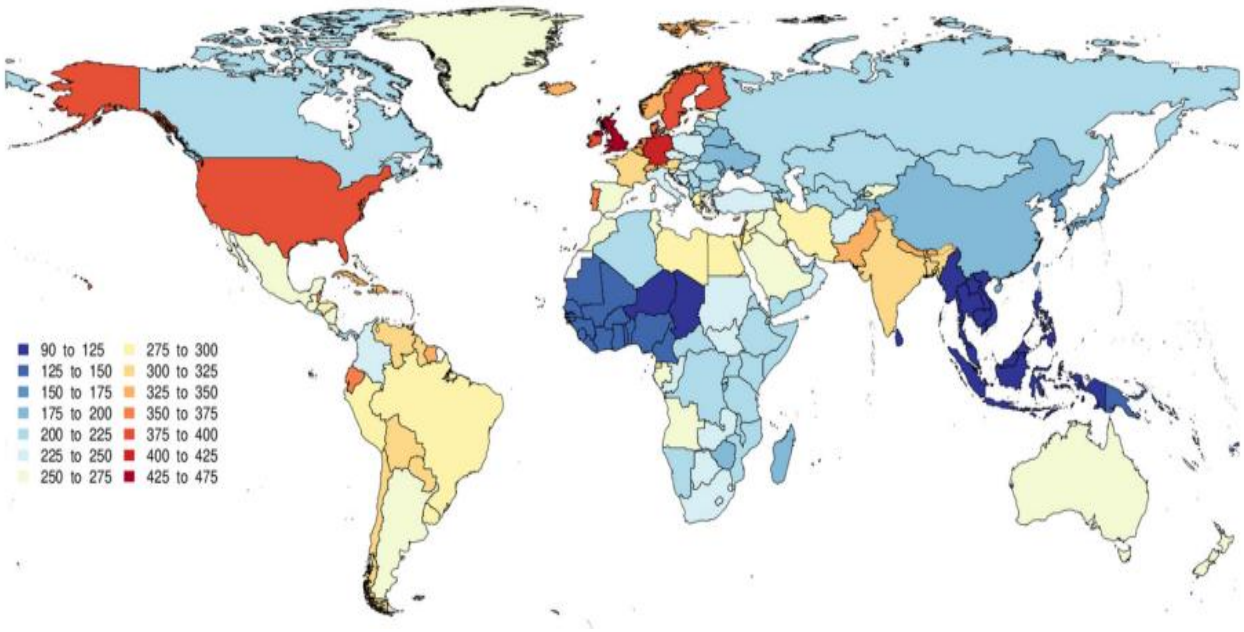

Figure 1. Age-standardized prevalence rate (per 100,000), 2017 ***(7)***.

According to the Global Burden of Disease (GBD) 2019 study, there were 18.6 million prevalent cases of RA globally, with an age-standardized point prevalence of 224.2 per 100,000 population and an age-standardized incidence rate of 13.0 per 100,000 and a disability-adjusted life-years (DALYs) rate of 39.6 per 100,000 population. In Egypt, there were 84.3 thousand prevalent cases of RA, with an age-standardized point prevalence of 98.1 per 100,000 population and an age-standardized incidence rate of 5.9 per 100,000. In addition, the rate of regional DALYs due to RA was 14.2 per 100,000 ***(7)***.

1.2 Etiology and risk factors:

The disease etiology remains unknown ***(8)***. Development of RA is significantly influenced by several genetic variables such as family genetic susceptibility, shared epi-tope, and Human Leucocyte Antigen-DR isotype (HLA-DR) genes, as well as several environmental and lifestyle factors, including infections, atmospheric agents, diet, hormonal factors, smoking, periodontal and lung diseases ***(9, 10)***.

1.3 Pathogenesis of RA:

According to evidence, there are many stages in the development of RA, including an asymptomatic period associated with genetic risk, a pre-clinical stage during which RA-related antibodies can be found, and a clinical stage during which inflammatory arthritis signs and symptoms appear ***(11)***.

1.4 Clinical features of RA:

Rheumatoid arthritis primarily affects the lining of the synovial joints which results in joint pain, swelling, rigidity, deformity, and function obstacles ***(12)***. It may also have extra-articular manifestations, with involvement of the skin, blood vessels, and internal organs ***(13)***. Long-term, it results in a considerable reduction in life quality and an increase in morbidity and mortality rate ***(14)***. Early referral, ideally to specialized early arthritis clinics, is essential to achieving a more rapid assessment of individuals with early-onset signs and symptoms of inflammatory arthritis ***(15)***.

1.5 Diagnosis:

The patient's medical history, laboratory results, physical examination, and radiographic information are all necessary to make the diagnosis of RA. Patient characteristics including age, gender, and ethnicity are essential since they are associated with disease risk and severity ***(16)***.

1.5.1 Diagnostic Criteria:

The American College of Rheumatology (ACR) issued a set of criteria used for differentiating RA from other inflammatory arthritis. The 1987 ACR classification criteria and the 2010 ACR/ European League Against Rheumatism (EULAR) classification criteria as shown in (**table 1)** ***(17, 18)***.

Table 1. The 1987 ACR classification criteria and the 2010 ACR/EULAR classification criteria for RA ***(19).***

	1987 classification criteria (parameters)	**2010 classification criteria (parameters and points)**
Entry criterion	None	(1) Patient with at least one joint with definite clinical synovitis (swelling) (2) Synovitis is not better explained by another disease.
Criteria	Morning stiffness (at least one hour)	Joint involvement: 1 large joint =0 2-10 large joints =1 1-3 small joints =2 4-10 small joints =3 >10 small joints =5
	Arthritis of three or more joint areas	Serology rheumatoid factor (RF) and Anti-citrullinated protein antibodies (ACPA) negative =0 Low positive RF or ACPA =2 High positive RF or ACPA =3
	Arthritis of hand joints (1 or more swollen joints)	Acute phase reactants: Normal=0 Elevated C-reactive protein (CRP) or erythrocyte sedimentation rate (ESR) =1
	Symmetric arthritis	Duration of symptoms: <6 weeks=0 >6 weeks=1
	Rheumatoid nodules	
	Serum RF	
	Radiographic changes	
Positivity	Criteria are fulfilled if 4 out of 7 parameters are present	Criteria are fulfilled if a patient has ≥6 points

1.5.2 Imaging tests (Radiology):

Conventional radiography (CR) imaging is routinely used for the assessment of joint destruction and the determination of disease outcomes. Radiographic abnormalities in the early stages of the disease are not always visible, but if the inflammation is severe, X-rays can show cartilage loss and joint erosions ***(20)***. Both musculoskeletal ultrasonography (MSUS) and magnetic resonance imaging (MRI) are thought to be superior to computed radiography (CR) because they can detect articular changes earlier than CR and without the use of ionizing radiation. However, MRI and MSUS require highly skilled staff, radiologists, and/or rheumatologists, and are time-consuming procedures ***(21)***.

1.5.3 Diagnostic Tests:

Both anti-cyclic citrullinated peptide antibodies (anti-CCP) and rheumatoid factor (RF) are sensitive laboratory markers for the diagnosis of RA, and anti-CCP antibody is more specific for RA disease. ESR and CRP are significant auxiliary markers for RA diagnosis even though they are nonspecific for this disease. For the accurate diagnosis of RA, simultaneous measurement of RF, anti-CCP antibody, CRP, and ESR is beneficial ***(22)***.

1.5.4 Measurement of disease activity:

Disease activity in RA is commonly measured using a disease activity score in 28 joints (DAS-28) ***(23)***. The DAS-28 includes the evaluation of 28 swollen joints (SJC-28) and tender joint counts (TJC-28), ESR, CRP, and patient's global health status on a 0–100 visual analogous scale (VAS) to calculate a score. The most widely used is the DAS28, which includes either CRP or ESR. It has been demonstrated that in clinical care and trials, a subset of the 28 named joints is just as valid and trustworthy as more comprehensive joint counts ***(24)***.

Clinical remission is defined as DAS28 <2.6, low disease activity DAS28 < 3.2, medium DAS28 from 3.2 to 5.1, and high disease activity has a value of DAS28 > 5.1 ***(25)***.

2. Methods

We performed a search on MEDLINE, which is the primary component of PubMed®, part of the Entrez series of databases provided by the US National Library of Medicine National Center for Biotechnology Information (NCBI). We used the keywords "Rheumatoid arthritis",

"MicroRNAs" and "RA diagnosis". We restricted results to papers published from 2015 to 2023 and published in English. Articles were screened for their relevance concerning miRNA participation in RA and excluded studies about other autoimmune diseases. Supplementary material concerning RA pathophysiology was included when necessary.

3. MicroRNAs

In *Caenorhabditis elegans*, the first miRNA was discovered and demonstrated to play a regulatory role in 2001. More miRNAs from various animal and plant species were reported immediately following this discovery. The identification of these small RNA molecules revolutionized our knowledge of how genes are regulated post-transcriptionally, and numerous research groups have since focused heavily on miRNAs ***(26)***.

A person's susceptibility to developing RA may be influenced by the genetic variance of certain miRNA genes. Additionally, it has been found that RA patients have altered expression of several miRNAs in a variety of cells, tissues, and bodily fluids ***(27)***. As a result, miRNAs have received a lot of attention in recent RA epigenetics research and have been suggested as biomarkers for diagnosis, prognosis, and therapy response in several disorders ***(28)***.

MicroRNA is a member of the endogenous small non-coding RNA family that is transcribed from genomic sequences and cleaved into miRNA precursor, to produce mature miRNA with a length of about 22 nucleotides ***(29)***. It is involved in the posttranscriptional regulation of gene expression by one of two mechanisms; the first is suppression of mRNA translation and the second is degradation of mRNA ***(30)***.

It has been proved that miRNAs play a vital role in numerous cellular processes, including cell cycle progression, cell differentiation, apoptosis, and autoimmune diseases ***(31)***. Recent research has confirmed that miRNAs play a significant role in RA, and the dysregulation in miRNA expression appears to play a role in the disease's molecular mechanisms ***(32)***.

3.1 Nomenclature:

Under a standard nomenclature system, miRNAs are identified using the "miR" prefix and a distinct characteristic number that frequently reflects the order of discovery (for example, miR-125). The uncapitalized prefix ''mir-'' stands for the pre-miRNA, while a capitalized ''miR-'' stands for the mature form. MiRNAs with almost similar sequences that differ by just one or

two nucleotides have the same number followed by a lower-case letter (for example, miR-125a and miR-125b). An additional dash-number suffix, such as (miR-146a-1 and miR146a-2) is used to identify miRNAs for which the mature sequences are 100% identical but are found in distinct locations in the genome ***(33)***.

To identify the species, an additional three letters are added to the prefix. For instance, Homo sapien-miR-123 (hsa-miR-123) is a human miRNA and ovis aries-miR-123 (oar-miR-123) is a sheep miRNA ***(34)***.

3.2 MiRNAs Biogenesis and mode of action:

MicroRNA biogenesis starts with the processing of RNA polymerase II/III transcripts post- or co-transcriptionally and the production of capped and polyadenylated long primary transcripts (pri-miRNA). Sometimes miRNAs are transcribed as one long transcript called clusters, which may have similar seed regions, in which case they are considered a family ***(35).***

In the next step, pri-miRNAs are further processed by the complex composed of RNase III Drosha and its RNA-binding protein component, DiGeorge syndrome critical region 8 (DGCR8) in the nucleus. pre-miRNAs (about 70 nucleotides in length) are emerged, and transported to the cytoplasm by exportin-5 (EXP-5) with a characteristic stem-loop structure ***(36).***

Another RNase III endonuclease (Dicer), along with its partner trans activator RNA binding protein (TRBP) digests the pre-miRNAs after exporting to produce the mature miRNA/miRNA* duplex that is composed of 20-22 nucleotides ***(37).***

The "passenger" strand (miRNA*) is released and destroyed after the duplex is unwounded by a helicase, and the miRNA "guide" strand, currently known as the 5′ terminals, is then incorporated into the RNA-induced silencing complex (RISC), (**figure 2)** ***(38)***.

The miRNA molecule guides the RISC complex to the three prime untranslated regions (3’-UTR) in the target mRNA (“templates”). The interaction between miRNA/ RISC and its target mRNA represses the translation process. Therefore, miRNAs are posttranscription regulators ***(36)***.

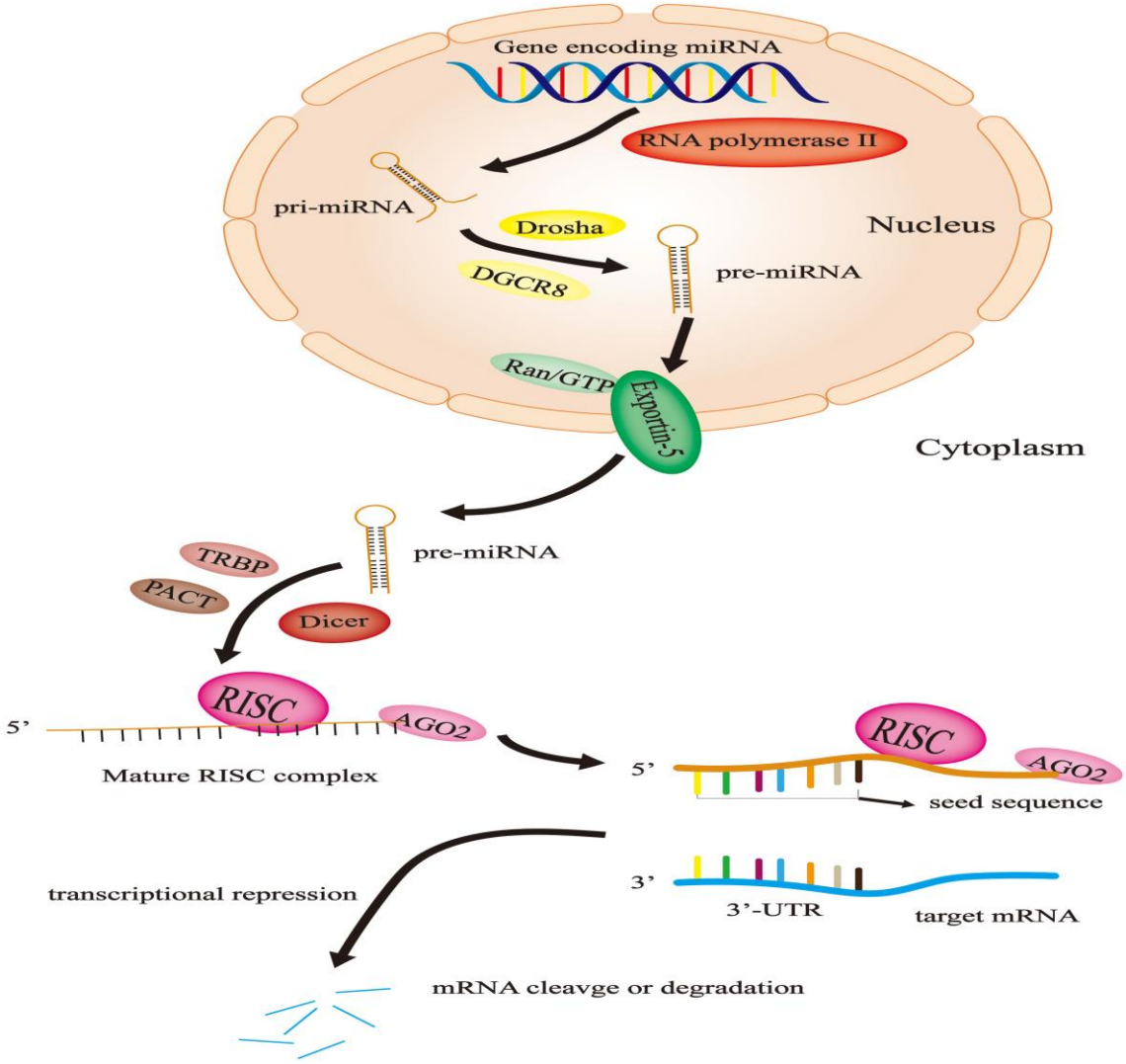

Figure 2. MicroRNA biogenesis and mode of action ***(39)*.**
DGCR8: DiGeorge syndrome critical region 8; TRBP: trans activator RNA binding protein; RISC: RNA induced silencing complex.

The critical region for miRNA binding is nucleotides 2-8 from the 5' end of the miRNA, called the 'seed region', which binds to its target site on a given mRNA by Watson-Crick complementarily ***(40)***.

3.3 Function of miRNAs:

3.3.1 Physiologically:

MicroRNA encoding sequences account for 1–3% of the mammalian genome; over 1900 miRNAs have been identified to play important regulatory roles and are included in almost all

physiological processes, including cellular growth, proliferation, differentiation; metabolism; and homeostasis ***(41).***

They participate in cell-to-cell communication and control a variety of cellular functions and signaling pathways. For instance, in response to tissue damage, miR-126 is delivered to vascular smooth muscle cells in endothelial cell-derived apoptotic bodies, where it facilitates the production of the (C-X-C motif) ligand 12 chemokines to recruit progenitor cells and promote vascular protection ***(42).***

In addition, some studies have associated miRNAs with the immune system. MiRNAs are involved in innate & adaptive immunity and defense against both RNA and DNA viruses ***(43).***

3.3.2 Pathologically:

Alterations of miRNA are involved in many diseases' initiation and progression. This alternation may be due to expression disorders, gene mutations, or natural genetic variants that may cause a single nucleotide mismatch between miRNA and its target site. This mismatch can change the efficacy and thermodynamics of miRNA ***(42)***.

MicroRNAs are involved in disease pathogenesis including; microbial infection, skin diseases, neurological diseases, cancer, CVDs, and diabetes ***(44)***.

In addition, The miRNA network is increasingly investigated in autoimmune diseases such as systemic lupus erythematosus (SLE) ***(45)***, RA ***(46)***, Addison disease ***(47),*** and Sjogren's syndrome (SS) ***(48)***.

3.4 Clinical value of miRNAs:

A growing number of studies point to the significant value of miRNAs as biomarkers for pathogenic disorders, drug resistance regulators, and/or therapeutics for human health problems ***(49)***.

They are present in various tissues, cells, organs, and body fluids, e.g., serum, plasma, urine, breast milk, saliva, tears, semen, and others. In contrast to conventional theories on the stability of extracellular RNA, circulating miRNAs have been demonstrated to be very durable in situations of severe pH and temperature and resistant to RNase activity ***(50)***. Consequently, miRNA molecules emerged as new biomarkers for diagnosis, prognosis, and predicting patients' response to treatment ***(51)***.

There are several examples of that such as their ability to behave as not only oncogenes but also tumor-suppressive genes in human malignancies ***(52)***. Additionally, they regulate particular host cell functions and promote the infection process ***(50)***.

Targeting miRNA has also been the focus of recent therapeutic studies, it was proven that through the dense mesochondrium, chondrocyte-affinity peptide-exosomes carry miR-140 to deep cartilage areas, inhibit cartilage-degrading proteases, and relieve osteoarthritis (OA) in a rat model, suggesting a possible organelle-based, cell-free therapy for OA ***(53)***.

4. MiRNAs and RA:

The key to effective treatment is early diagnosis, especially in patients who have risk factors for a poor prognosis (such as the presence of autoantibodies, high disease activity, and early joint destruction) ***(54)***. This research aims to provide an expert review of miRNAs as diagnostic biomarkers for RA.

MiR-21

It was found that miR-21 was upregulated in peripheral blood and plasma of the RA group when compared to HCs ***(55-57)***. *Xiong et al.* showed significant elevation in miR-21 expression in FLSs and synovial tissue in RA patients and silencing of miR-21 could suppress FLSs invasiveness through TGFβ1/Smad4/7 signaling pathway ***(58)***. In contrast, RA patients were shown to have lower levels of miR-21 in synovial fluid's CD4+T helper cells than controls. In addition, the reduction in miR-21 expression may disrupt the formation of Th17/Treg cells in RA patients ***(59)***. In PBMC of RA patients, miR-21 was observed to be considerably lower than those in HCs ***(60).*** In addition, overexpression of miR-21 was found to reduce IL-6 and IL-8 levels and alleviate RA symptoms of RA through Wnt signaling pathway downregulation ***(61)***.

MiR-22

Tang et al. examined the diagnostic value of circulating miR-22-3p in early-diagnosed RA patients that showed upregulation in the plasma of the RA group ***(62, 63)***. The levels of miR-22 in serum were increased in the susceptible individuals (pre-RA) and this implied that miR-22 might be used to predict RA development in individuals with positive ACPAs ***(64)***. On the contrary, it has been reported that decreased miR-22-3p in RA synovial tissue promoted FLS proliferation and proinflammatory cytokine production ***(63)***.

MiR-23b

Rheumatoid arthritis patients' plasma and synovial tissues were found to have higher levels of miR-23b when compared to HCs ***(65)***. In other studies, the expression of miR-23b was downregulated in synovial tissue of patients early diagnosed with RA ***(60)***.

MiR-96

Abdallah et al. Reported that miR-96-5p could be used as a diagnostic biomarker for RA. Significant elevation in miR-96 expression has been shown in the serum of early diagnosed RA patients compared to controls that could negatively affect the expression of FOXO1 ***(66)***. Furthermore, miR-96 expression correlated significantly with disease activity measures of RA (DAS28, SJC, and TJC) ***(66)***. It has been found also that miR-96 alleviates inflammatory responses by targeting NAMPT and regulating the NF-κB pathway ***(67).*** More studies should be performed to assess miR-96 expression in other specimens such as FLS, PBMCs, and synovial tissues.

MiR-125a, miR-125b

Dysregulation of miR-125a and miR-125b has been shown in the peripheral blood of RA patients. Declined expression levels of miR-125a-3p ***(57)*** and raised levels of miR-125b and miR-125a-5p were determined in the serum/plasma of RA patients ***(54, 55)***. This is against *Al-Rawaf et al.* who found that miR-125 b significantly reduced in RA patients' serum levels compared to female control subjects. Moreover, miR-125 b expression correlated significantly with disease activity measures of RA (DAS28, SJC, TJC, PGA Score, ESR, CRP, and HAQ-DI) and pain intensity ***(68)***. It was found also that the combination between circulating miR-24 and miR-125a increase the potency of RA diagnosis ***(69)***. Another study illustrated that the expression of miR-125 in RA synovial cells and tissues was significantly downregulated ***(70)***. In addition, miR-125a-3p was found to be downregulated in RA-FLS and RA-tissues, which may have a negative impact on the proliferation and inflammatory response of RA-FLS ***(71)***.

MiR-132

Several studies have shown that the level of miR-132 is increased in blood cells as compared to healthy controls due to its importance as a modulator of the disease pathology in RA ***(72, 73)***. In PBMC, miR-132 was reported to be significantly increased in RA patients in comparison to controls ***(74)***. However, other studies showed downregulation in the level of miR-132 in serum/plasma from RA patients ***(57, 75)***.

MiR-146a

One of the most researched miRNAs is miR-146a. MiR-146a is elevated in RA peripheral blood ***(76),*** serum ***(77)***, CD4+ T cells ***(78),*** and synovial tissue of the RA group in comparison to the control group ***(60)***. However, it has also been noted that miR-146a levels in RA FLS have decreased, suggesting that this miRNA has anti-inflammatory effects on FLS ***(79)***. Additionally, an increase in miR-146a has been linked to the expression of interleukin (IL)-17 and in particular the early stages of RA ***(80)***.

MiR-155

The majority of research in RA revealed elevated levels of miR-155 in various cell types or tissues. Comparing the RA group to controls, MiR-155 serum expression was higher, and it had been associated with TNF- and IL-1 levels ***(81)***. *Y. Wang et al.* demonstrated that miR-155 overexpression reduced FOXO3a expression in FLS cells and enhanced FLS secretion of the inflammatory cytokines IL 1, IL 6, and TNF-α ***(82)***. Additionally, synovial fluid monocytes (SFM), PBMCs, and RASF have higher levels of miR-155 expression, which causes an increase of monocytes and macrophages in the synovial tissue as well as an excess of pro-inflammatory cytokines ***(83)***. Furthermore, it was found that RA patients' whole blood ***(72)***, CD68+ synovium macrophages ***(84),*** and synovial tissue all had high levels of miR-155 expression ***(80)***. On the other hand, *Zhou et al.* Investigated downregulation of miR-155 expression in regulatory T cells (Tregs) of RA patients ***(85).*** *Kolarz et al.* also that RA patients' plasma had lower levels of miR-155 than in controls ***(83)***.

MiR-203

In a study by *Wang, Zhao, et al.* miR-203 was proven to be upregulated in RASFs and synovial tissues of the RA group compared to controls, and miR-203 suppression reduced cell proliferation and inflammation in RASFs ***(86)***. More studies are needed to declare the role of miR-203 as a diagnostic biomarker for RA.

MiR-223

Numerous studies provide evidence that miR-223 is much more abundant in RA patients' serum, plasma, and PBMCs than in controls, suggesting that miR-223 may be correlated to the development, progression, and severity of RA ***(87, 88)***. In contrast, *Dunaeva et al.* demonstrated significantly lower levels of miR-223 in the sera of patients with early diagnosed RA in comparison with established RA patients and healthy controls considering miR-223 as a

promising biomarker in early diagnosis ***(89)***. As a positive inflammatory regulator, miR-223 has also been shown to be elevated in macrophages, T-cells, and synovial tissue, and silencing of miR-223 led to a reduction in disease severity ***(80, 87, 90)***. *Kriegsmann et al.* reported also that miR-146a, miR-155, and miR-223 were significantly elevated in RA compared to OA synovial tissues thus these miRNAs might be used to differentiate RA from OA ***(80)***.

MiR-298

No more studies discussed the expression of miR-298 in RA. Early-stage RA patients' serum expression of miR-298 was proven to be higher when compared to healthy controls with AUC (0.94) and there was a significant positive correlation between miR-298 and Anti-CCP, ESR, and disease activity score so, it could be considered a promising biomarker for the detection of RA ***(66)***. In addition, the activation of macrophages with TNF-α has been shown to increase the expression of miR-298. ***(79)***.

MiR-451

It is reported that the miRNA-451 expression level is lower in the peripheral neutrophils of RA patients than in normal control ***(73)***. *Prajzlerová et al.* confirmed higher expression of miR-451 in PBMC from ACPA-positive early diagnosed RA- individuals compared to HC ***(91)***. In addition, miR-451 was reported also to have an up-regulation in circulating T cells of RA patients in comparison to controls and there was a positive correlation between increased expression of miR-451 in T cells of RA patients and DAS28, ESR levels, and serum levels of interleukin-6 ***(60)***. *Wang et al.* suggested also that miR-451 overexpressed in synovial fibroblasts isolated from RA patients compared to controls, which explains how this inhibits the proliferation of these cells and the production of cytokines in RA ***(92)***.

MiR-498

According to a prior study, RA patients' cartilage tissues had considerably less miR-498 expression than control specimens ***(93)***. It was found also that miR-498 expression was reduced and that STAT3 was increased in the PMBCs of RA patients ***(94)***. In $CD4^+$ T cells from peripheral blood and synovial fluid of RA patients, downregulation of miR-498 was recognized ***(73)***. Furthermore, *Dai et al.* assessed the diagnostic accuracy of the significantly regulated miR-498 and noticed significant downregulation in the bone tissue of RA patients versus controls with AUC= 0.769 for miR-498 ***(95)***.

Table 2. Dysregulation of MiRNAs expression in RA.

MicroRNAs	**miRNA expression**	**Localization (Cells/Organ of RA)**	**References**
MiR-21	• ↑ • ↑ • ↑ • ↓ • ↓	• Peripheral blood • Plasma • Synovial tissue & FLSs • CD4 Th cells of synovial fluid • PBMCs	(55) (57) (58) (59) (60)
MiR-22	• ↑ • ↑ • ↓	• Plasma • Serum • Synovial tissue	(62) (64) (63)
MiR-23b	• ↑ • ↑ ↓	• Plasma • Synovial tissue	(65) (65) (60)
MiR-96	• ↑	• Serum	(66)
MiR-125a-3p MiR-125a-5p	• ↓ • ↓ • ↑	• Serum/Plasma • Synovial tissue & FLSs • Serum/Plasma	(57) (70, 71) (55)
MiR-125b	• ↑ • ↓	• Serum/Plasma • Serum	(54) (68)
MiR-132	• ↑ • ↑ • ↓	• Peripheral blood • PBMCs • Serum/Plasma	(72, 73) (74) (57, 75)
MiR-146a	• ↑ • ↑ • ↑ • ↑ • ↓	• Peripheral blood • Serum • Synovial tissue • CD4 Th cells • FLSs	(76) (77) (60) (78) (79)
MiR-155	• ↑ • ↑ • ↑ • ↑ • ↑ • ↑ • ↓ • ↓	• Serum • FLSs • SFM, RASF and PBMCs • Synovial tissue • CD68+ synovium macrophages • Peripheral blood • T cells (Tregs) • Plasma	(81) (82) (83) (80) (84) (72) (85) (83)
MiR-203	• ↑	• Synovial tissue RASFs	(86)
MiR-223	• ↑ • ↑ • ↑ • ↑ • ↓	• Serum/Plasma • PBMCs T cells • Macrophages • Synovial tissue • Serum	(88) (87) (90) (80) (89)
MiR-298	• ↑	• Serum	(66)
MiR-451	• ↓ • ↑	• Peripheral neutrophils • PBMCs	(73) (91)

	• ↑ • ↑	• Circulating T cells • Synovial fibroblasts	(60) (92)
MiR-498	• ↓ • ↓ • ↓	• Cartilage tissues • PBMCs • peripheral blood and synovial fluid $CD4^+$ T cells	(93) (94) (73)

FLSs: fibroblast-like synoviocytes, PBMCs: peripheral blood mononuclear cells, SFM: synovial fluid monocytes, RASF: rheumatoid arthritis synovial fibroblasts.

5. Conclusion

Identification of RA at initial presentation and treatment at an earlier stage can affect the disease course and prevent the development of progressive complications. clinical or laboratory parameters at the onset of arthritis are still not sensitive enough to identify early RA. This study predicts that several microRNAs can be considered promising diagnostic biomarkers for RA; some of them may be useful for the diagnosis of early rheumatoid arthritis such as (miR-22, miR-96, miR-146, miR-223, miR-298 and miR-451) so, they are possible biomarkers for early diagnosis. MiR-22 may also predict the risk of RA in susceptible individuals (pre-RA phase). Moreover, certain circulating miRNAs were found to be correlated with the disease activity of RA. For example, serum expression of miR-96, miR-125, miR-223, miR-298 and miR-451 was shown to correlate with RA disease activity indexes, such as TJC, SJC and 28-DAS28 therefore, they are considered markers of disease activity. In addition, the expression levels of miR-146a, miR-155 and miR-223 were significantly increased in the synovial fluid of RA patients, which may differentiate RA from OA. On the other side, expression levels of miR-125 and miR-223 can be upregulated and also downregulated in RA serum/plasma, which is controversial and need to be re-studied. Also, few studies were performed on miR-23, miR-96, miR-203 and miR-298 so they require additional research to support that. Despite several advantages of miRNAs as potential biomarkers for RA, there are some challenges to miRNAs application for diagnostic purposes. One of them is that the specificity and sensitivity of a single miRNA as a biomarker of RA is generally low and it is preferable to use a set of several miRNAs or the combination of miRNAs such as (miR-24 and miR-125a) with other parameters to get an effective diagnostic tool. In addition, risk of false-positive results, as most of the miRNAs studied are non-specific for RA, and be expressed in other autoimmune disorders.

- **Conflict of Interest**

The authors declare no conflict of interest.

6. References

[1] McInnes IB, Schett G. Pathogenetic insights from the treatment of rheumatoid arthritis. The Lancet. 2017;389(10086):2328-37.

[2] Wang K, Zhang D, Liu Y, Wang X, Zhao J, Sun T, et al. Traditional Chinese medicine formula Bi-Qi capsule alleviates rheumatoid arthritis-induced inflammation, synovial hyperplasia, and cartilage destruction in rats. Arthritis Research & Therapy. 2018;20:1-12.

[3] Bullock J, Rizvi SA, Saleh AM, Ahmed SS, Do DP, Ansari RA, et al. Rheumatoid arthritis: a brief overview of the treatment. Medical Principles and Practice. 2019;27(6):501-7.

[4] Dargham SR, Zahirovic S, Hammoudeh M, Al Emadi S, Masri BK, Halabi H, et al. Epidemiology and treatment patterns of rheumatoid arthritis in a large cohort of Arab patients. PloS one. 2018;13(12):e0208240.

[5] Almutairi K, Nossent J, Preen D, Keen H, Inderjeeth C. The global prevalence of rheumatoid arthritis: a meta-analysis based on a systematic review. Rheumatology international. 2021;41(5):863-77.

[6] Safiri S, Kolahi AA, Hoy D, Smith E, Bettampadi D, Mansournia MA, et al. Global, regional and national burden of rheumatoid arthritis 1990–2017: a systematic analysis of the Global Burden of Disease study 2017. Annals of the rheumatic diseases. 2019;78(11):1463-71.

[7] Mousavi SE, Nejadghaderi SA, Khabbazi A, Alizadeh M, Sullman MJ, Kaufman JS, et al. The burden of rheumatoid arthritis in the Middle East and North Africa region, 1990–2019. Scientific Reports. 2022;12(1):19297.

[8] Volkov M, van Schie KA, van der Woude D. Autoantibodies and B Cells: The ABC of rheumatoid arthritis pathophysiology. Immunological reviews. 2020;294(1):148-63.

[9] England B, Mikuls TR. Epidemiology of, risk factors for, and possible causes of rheumatoid arthritis. 2020.

[10] Okada Y, Eyre S, Suzuki A, Kochi Y, Yamamoto K. Genetics of rheumatoid arthritis: 2018 status. Annals of the rheumatic diseases. 2019;78(4):446-53.

[11] Petrovská N, Prajzlerová K, Vencovský J, Šenolt L, Filková M. The pre-clinical phase of rheumatoid arthritis: from risk factors to prevention of arthritis. Autoimmunity Reviews. 2021;20(5):102797.

[12] Guo Q, Wang Y, Xu D, Nossent J, Pavlos NJ, Xu J. Rheumatoid arthritis: pathological mechanisms and modern pharmacologic therapies. Bone research. 2018;6(1):1-14.

[13] MATSUSHITA M, YAMAJI K, TAMURA N. Extra-articular manifestations of rheumatoid arthritis. Juntendo Medical Journal. 2020;66(1):21-6.

[14] Fazal SA, Khan M, Nishi SE, Alam F, Zarin N, Bari MT, et al. A clinical update and global economic burden of rheumatoid arthritis. Endocrine, Metabolic & Immune Disorders-Drug Targets (Formerly Current Drug Targets-Immune, Endocrine & Metabolic Disorders). 2018;18(2):98-109.

[15] Burmester GR, Pope JE. Novel treatment strategies in rheumatoid arthritis. The Lancet. 2017;389(10086):2338-48.

[16] van der Woude D, van der Helm-van AH. Update on the epidemiology, risk factors, and disease outcomes of rheumatoid arthritis. Best practice & research Clinical rheumatology. 2018;32(2):174-87.

[17] Arnett FC, Edworthy SM, Bloch DA, Mcshane DJ, Fries JF, Cooper NS, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis & Rheumatism: Official Journal of the American College of Rheumatology. 1988;31(3):315-24.

[18] Aletaha D, Neogi T, Silman AJ, Funovits J, Felson DT, Bingham III CO, et al. 2010 rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Arthritis & rheumatism. 2010;62(9):2569-81.

[19] van der Helm-van AH, Zink A. What is rheumatoid arthritis? Considering consequences of changed classification criteria. BMJ Publishing Group Ltd; 2017.

[20] Kgoebane K, Ally MM, Duim-Beytell MC, Suleman FE. The role of imaging in rheumatoid arthritis. SA Journal of Radiology. 2018;22(1):1-6.

[21] Drosos AA, Pelechas E, Voulgari PV. Conventional radiography of the hands and wrists in rheumatoid arthritis. What a rheumatologist should know and how to interpret the radiological findings. Rheumatology international. 2019;39(8):1331-41.

[22] Shen R, Ren X, Jing R, Shen X, Chen J, Ju S, et al. Rheumatoid factor, anti-cyclic citrullinated peptide antibody, C-reactive protein, and erythrocyte sedimentation rate for the clinical diagnosis of rheumatoid arthritis. Laboratory medicine. 2015;46(3):226-9.

[23] Hamann PD, Shaddick G, Hyrich K, Green A, McHugh N, Pauling JD, et al. Gender stratified adjustment of the DAS28-CRP improves inter-score agreement with the DAS28-ESR in rheumatoid arthritis. Rheumatology. 2019;58(5):831-5.

[24] Orr CK, Najm A, Young F, McGarry T, Biniecka M, Fearon U, et al. The utility and limitations of CRP, ESR and DAS28-CRP in appraising disease activity in rheumatoid arthritis. Frontiers in medicine. 2018;5:185.

[25] Forslind K, Svensson B. MRI evidence of persistent joint inflammation and progressive joint damage despite clinical remission during treatment of early rheumatoid arthritis. Scandinavian journal of rheumatology. 2016;45(2):99-102.

[26] Budak H, Bulut R, Kantar M, Alptekin B. MicroRNA nomenclature and the need for a revised naming prescription. Briefings in functional genomics. 2016;15(1):65-71.

[27] Long H, Wang X, Chen Y, Wang L, Zhao M, Lu Q. Dysregulation of microRNAs in autoimmune diseases: Pathogenesis, biomarkers and potential therapeutic targets. Cancer letters. 2018;428:90-103.

[28] Evangelatos G, Fragoulis GE, Koulouri V, Lambrou GI. MicroRNAs in rheumatoid arthritis: From pathogenesis to clinical impact. Autoimmunity Reviews. 2019;18(11):102391.

[29] Letafati A, Najafi S, Mottahedi M, Karimzadeh M, Shahini A, Garousi S, et al. MicroRNA let-7 and viral infections: focus on mechanisms of action. Cellular & Molecular Biology Letters. 2022;27(1):1-47.

[30] Vos PD, Leedman PJ, Filipovska A, Rackham O. Modulation of miRNA function by natural and synthetic RNA-binding proteins in cancer. Cellular and Molecular Life Sciences. 2019;76(19):3745-52.

[31] Wu J, Fan W, Ma L, Geng X. miR-708-5p promotes fibroblast-like synoviocytes' cell apoptosis and ameliorates rheumatoid arthritis by the inhibition of Wnt3a/β-catenin pathway. Drug design, development and therapy. 2018;12:3439.

[32] Croia C, Bursi R, Sutera D, Petrelli F, Alunno A, Puxeddu I. One year in review 2019: pathogenesis of rheumatoid arthritis. Clin Exp Rheumatol. 2019;37(3):347-57.

[33] Gonzalez P, Li G, Qiu J, Wu J, Luna C. Role of microRNAs in the trabecular meshwork. Journal of ocular pharmacology and therapeutics. 2014;30(2-3):128-37.

[34] Baulina N, Kulakova O, Favorova O. MicroRNAs: the role in autoimmune inflammation. Acta Naturae (англоязычная версия). 2016;8(1 (28)).

[35] O'Brien J, Hayder H, Zayed Y, Peng C. Overview of microRNA biogenesis, mechanisms of actions, and circulation. Frontiers in endocrinology. 2018;9:402.

[36] Olejniczak M, Kotowska-Zimmer A, Krzyzosiak W. Stress-induced changes in miRNA biogenesis and functioning. Cellular and molecular life sciences. 2018;75(2):177-91.

[37] Andersson KM, Turkkila M, Erlandsson MC, Bossios A, Silfverswärd ST, Hu D, et al. Survivin controls biogenesis of microRNA in smokers: a link to pathogenesis of rheumatoid arthritis. Biochimica et Biophysica Acta (BBA)-Molecular Basis of Disease. 2017;1863(3):663-73.

[38] Treiber T, Treiber N, Plessmann U, Harlander S, Daiß J-L, Eichner N, et al. A compendium of RNA-binding proteins that regulate microRNA biogenesis. Molecular cell. 2017;66(2):270-84. e13.

[39] Yang Y, Meng W-J, Wang Z-Q. MicroRNAs (miRNAs): Novel potential therapeutic targets in colorectal cancer. Frontiers in Oncology. 2022;12:1054846.

[40] Riffo-Campos ÁL, Riquelme I, Brebi-Mieville P. Tools for sequence-based miRNA target prediction: what to choose? International journal of molecular sciences. 2016;17(12):1987.

[41] Wang J, Chen J, Sen S. MicroRNA as biomarkers and diagnostics. Journal of cellular physiology. 2016;231(1):25-30.

[42] Wojciechowska A, Braniewska A, Kozar-Kamińska K. MicroRNA in cardiovascular biology and disease. Advances in clinical and experimental medicine: official organ Wroclaw Medical University. 2017;26(5):865-74.

[43] Albanese M, Tagawa T, Buschle A, Hammerschmidt W. MicroRNAs of Epstein-Barr virus control innate and adaptive antiviral immunity. Journal of virology. 2017;91(16):e01667-16.

[44] Ali Syeda Z, Langden SSS, Munkhzul C, Lee M, Song SJ. Regulatory mechanism of microRNA expression in cancer. International journal of molecular sciences. 2020;21(5):1723.

[45] Hong S-M, Liu C, Yin Z, Wu L, Qu B, Shen N. MicroRNAs in systemic lupus erythematosus: a perspective on the path from biological discoveries to clinical practice. Current rheumatology reports. 2020;22:1-9.

[46] Salehi E, Eftekhari R, Oraei M, Gharib A, Bidad K. MicroRNAs in rheumatoid arthritis. Clinical rheumatology. 2015;34(4):615-28.

[47] Isaacs LL. Whole adrenal extract for Addison's disease in the 1920s: Where is the cortisol? Medical Hypotheses. 2022;158:110731.

[48] Jin F, Hu H, Xu M, Zhan S, Wang Y, Zhang H, et al. Serum microRNA profiles serve as novel biomarkers for autoimmune diseases. Frontiers in immunology. 2018;9:2381.

[49] Hanna J, Hossain GS, Kocerha J. The potential for microRNA therapeutics and clinical research. Frontiers in genetics. 2019;10:478.

[50] Lukasik A, Zielenkiewicz P. Plant microRNAs—Novel players in natural medicine? International journal of molecular sciences. 2017;18(1):9.

[51] Silva SS, Lopes C, Teixeira A, De Sousa MC, Medeiros R. Forensic miRNA: potential biomarker for body fluids? Forensic Science International: Genetics. 2015;14:1-10.

[52] Yu N, Yong S, Kim HK, Choi YL, Jung Y, Kim D, et al. Identification of tumor suppressor miRNAs by integrative miRNA and mRNA sequencing of matched tumor–normal samples in lung adenocarcinoma. Molecular oncology. 2019;13(6):1356-68.

[53] Liang Y, Xu X, Li X, Xiong J, Li B, Duan L, et al. Chondrocyte-targeted MicroRNA delivery by engineered exosomes toward a cell-free osteoarthritis therapy. ACS Applied Materials & Interfaces. 2020;12(33):36938-47.

[54] Huang R-Y, Wu J-Q, Liu Z-H, Sun S-L. MicroRNAs in rheumatoid arthritis: what is the latest with regards to diagnostics? 2019;19(5):363-6.

[55] Rezaeepoor M, Pourjafar M, Tahamoli-Roudsari A, Basiri Z, Hajilooi M, Solgi G. Altered expression of microRNAs may predict therapeutic response in rheumatoid arthritis patients. International immunopharmacology. 2020;83:106404.

[56] Ciancio G, Ferracin M, Saccenti E, Bagnari V, Farina I, Furini F, et al. Characterisation of peripheral blood mononuclear cell microRNA in early onset psoriatic arthritis. Clin Exp Rheumatol. 2017;35(1):113-21.

[57] Churov AV, Oleinik EK, Knip M. MicroRNAs in rheumatoid arthritis: altered expression and diagnostic potential. Autoimmunity reviews. 2015;14(11):1029-37.

[58] Xiong G, Huang Z, Jiang H, Pan Z, Xie J, Wang S. Inhibition of microRNA-21 decreases the invasiveness of fibroblast-like synoviocytes in rheumatoid arthritis via TGFβ/Smads signaling pathway. Iranian Journal of Basic Medical Sciences. 2016;19(7):787.

[59] Jin S, Chen H, Li Y, Zhong H, Sun W, Wang J, et al. Maresin 1 improves the Treg/Th17 imbalance in rheumatoid arthritis through miR-21. Annals of the rheumatic diseases. 2018;77(11):1644-52.

[60] Huang R-Y, Wu J-Q, Liu Z-H, Sun S-L. MicroRNAs in rheumatoid arthritis: what is the latest with regards to diagnostics? Expert Review of Molecular Diagnostics. 2019;19(5):363-6.

[61] Liu X, Zhang Y, Ju W, Li C, Mu Y. MiR-21 relieves rheumatoid arthritis in rats via targeting Wnt signaling pathway. Eur Rev Med Pharmacol Sci. 2019;23(3 Suppl):96-103.

[62] Tang J, Lin J, Yu Z, Jiang R, Xia J, Yang B, et al. Identification of circulating miR-22-3p and let-7a-5p as novel diagnostic biomarkers for rheumatoid arthritis. Clin Exp Rheumatol. 2022;40(1):69-77.

[63] Zhang C, Fang L, Liu X, Nie T, Li R, Cui L, et al. miR-22 inhibits synovial fibroblasts proliferation and proinflammatory cytokine production in RASF via targeting SIRT1. Gene. 2020;724:144144.

[64] Ouboussad L, Hunt L, Hensor EM, Nam JL, Barnes N, Emery P, et al. Profiling microRNAs in individuals at risk of progression to rheumatoid arthritis. Arthritis research & therapy. 2017;19(1):1-9.

[65] Liu X, Ni S, Li C, Xu N, Chen W, Wu M, et al. Circulating microRNA-23b as a new biomarker for rheumatoid arthritis. Gene. 2019;712:143911.

[66] Abdallah GM, Sayed SM, Aly HM, Yahia MB, Mohamed NR. Assessment of MicroRNA (96) and MicroRNA (298) as Biomarkers for Diagnosis and Prognosis of Rheumatoid Arthritis in Egyptian Patients. Azhar International Journal of Pharmaceutical and Medical Sciences. 2023;3(1):32-43.

[67] Chen X, Chen Y, Dai L, Wang N. MiR-96-5p alleviates inflammatory responses by targeting NAMPT and regulating the NF-κB pathway in neonatal sepsis. Bioscience reports. 2020;40(7).

[68] Al-Rawaf HA, Alghadir AH, Gabr SA. Circulating microRNAs expression as predictors of clinical response in rheumatoid arthritis patients treated with green tea. Journal of Herbal Medicine. 2021;27:100363.

[69] Prajzlerová K, Šenolt L, Filková M. Is there a potential of circulating miRNAs as biomarkers in rheumatic diseases? Genes & Diseases. 2022.

[70] Liu K, Zhang Y, Liu L, Yuan Q. miR-125 regulates PI3K/Akt/mTOR signaling pathway in rheumatoid arthritis rats via PARP2. Bioscience reports. 2019;39(1).

[71] Wang Y, Yin Z, Zhang N, Song H, Zhang Q, Hao X, et al. MiR-125a-3p inhibits cell proliferation and inflammation responses in fibroblast-like synovial cells in rheumatoid arthritis by mediating the Wnt/β-catenin and NF-κB pathways via targeting MAST3. Journal of Musculoskeletal & Neuronal Interactions. 2021;21(4):560.

[72] Singh A, Patro PS, Aggarwal A. MicroRNA-132, miR-146a, and miR-155 as potential biomarkers of methotrexate response in patients with rheumatoid arthritis. Clinical rheumatology. 2019;38:877-84.

[73] Zakeri Z, Salmaninejad A, Hosseini N, Shahbakhsh Y, Fadaee E, Shahrzad MK, et al. MicroRNA and exosome: key players in rheumatoid arthritis. Journal of Cellular Biochemistry. 2019;120(7):10930-44.

[74] Salehi E, Eftekhari R, Oraei M, Gharib A, Bidad K. MicroRNAs in rheumatoid arthritis. Clinical rheumatology. 2015;34:615-28.

[75] Sujitha S, Rasool M. MicroRNAs and bioactive compounds on TLR/MAPK signaling in rheumatoid arthritis. Clinica Chimica Acta. 2017;473:106-15.

[76] Liu M, Ren T, Lin Z, Hua M. Upregulated miR-146a Expression in Peripheral Blood Relates to Th17 and Treg Imbalance in Elder Rheumatoid Arthritis Patients. Lifestyle Genomics. 2022;15(3):98-106.

[77] Elsayed HMA, Khater WS, Ibrahim AA, Hamdy MSE-d, Morshedy NA. MicroRNA-146a expression as a potential biomarker for rheumatoid arthritis in Egypt. Egyptian Journal of Medical Human Genetics. 2017;18(2):173-9.

[78] Shahriar A, Shiva GG-a, Ghader B, Farhad J, Hosein A, Parsa H. The dual role of mir-146a in metastasis and disease progression. Biomedicine & Pharmacotherapy. 2020;126:110099.

[79] Dudics S, Venkatesha S, Moudgil K. The micro-RNA expression profiles of autoimmune arthritis reveal novel biomarkers of the disease and therapeutic response. International journal of molecular sciences. 2018;19(8):2293.

[80] Kriegsmann M, Randau TM, Gravius S, Lisenko K, Altmann C, Arens N, et al. Expression of miR-146a, miR-155, and miR-223 in formalin-fixed paraffin-embedded synovial tissues of patients with rheumatoid arthritis and osteoarthritis. Virchows Archiv. 2016;469:93-100.

[81] Abdul-Maksoud R, Sediq A, Kattaia A, Elsayed W, Ezzeldin N, Abdel Galil S, et al. Serum miR-210 and miR-155 expression levels as novel biomarkers for rheumatoid arthritis diagnosis. British Journal of Biomedical Science. 2017;74(4):209-13.

[82] Wang Y, Feng T, Duan S, Shi Y, Li S, Zhang X, et al. miR-155 promotes fibroblast-like synoviocyte proliferation and inflammatory cytokine secretion in rheumatoid arthritis by targeting FOXO3a. Experimental and therapeutic medicine. 2020;19(2):1288-96.

[83] Kolarz B, Ciesla M, Dryglewska M, Rosenthal AK, Majdan M. Hypermethylation of the miR-155 gene in the whole blood and decreased plasma level of miR-155 in rheumatoid arthritis. PloS One. 2020;15(6):e0233897.

[84] Li H, Liu P, Gong Y, Liu J, Ruan F. Expression and function of miR-155 in rat synovial fibroblast model of rheumatoid arthritis. Experimental and Therapeutic Medicine. 2019;18(1):786-92.

[85] Zhou Q, Haupt S, Kreuzer JT, Hammitzsch A, Proft F, Neumann C, et al. Decreased expression of miR-146a and miR-155 contributes to an abnormal Treg phenotype in patients with rheumatoid arthritis. Annals of the rheumatic diseases. 2015;74(6):1265-74.

[86] Wang L, Zhao Q, Wang N, Ding Y, Kong L, Wang J. Circ_0000396 inhibits rheumatoid arthritis synovial fibroblast growth and inflammatory response via miR-203/HBP1 axis. Journal of Biological Research-Thessaloniki. 2021;28(1):1-11.

[87] Jiao P, Wang X-P, Luoreng Z-M, Yang J, Jia L, Ma Y, et al. miR-223: an effective regulator of immune cell differentiation and inflammation. International Journal of Biological Sciences. 2021;17(9):2308.

[88] Taha M, Shaker OG, Abdelsalam E, Taha N. Serum a proliferation-inducing ligand and MicroRNA-223 are associated with rheumatoid arthritis: diagnostic and prognostic implications. Molecular Medicine. 2020;26(1):1-9.

[89] Dunaeva M, Blom J, Thurlings R, Pruijn G. Circulating serum miR-223-3p and miR-16-5p as possible biomarkers of early rheumatoid arthritis. Clinical & Experimental Immunology. 2018;193(3):376-85.

[90] Aziz F. The emerging role of miR-223 as novel potential diagnostic and therapeutic target for inflammatory disorders. Cellular immunology. 2016;303:1-6.

[91] Prajzlerová K, Kryštůfková O, Hánová P, Horváthová V, Gregová M, Pavelka K, et al. High miR-451 expression in peripheral blood mononuclear cells from subjects at risk of developing rheumatoid arthritis. Scientific Reports. 2021;11(1):1-9.

[92] Wang Z-C, Lu H, Zhou Q, Yu S-M, Mao Y-L, Zhang H-J, et al. MiR-451 inhibits synovial fibroblasts proliferation and inflammatory cytokines secretion in rheumatoid arthritis through mediating p38MAPK signaling pathway. International journal of clinical and experimental pathology. 2015;8(11):14562.

[93] Li G, Tan W, Fang Y, Wu X, Zhou W, Zhang C, et al. circFADS2 protects LPS-treated chondrocytes from apoptosis acting as an interceptor of miR-498/mTOR cross-talking. Aging (Albany NY). 2019;11(10):3348.

[94] Xiang H-Y, Pan F, Yan J-Z, Hong L-Q, Zhang L-H, Liu Y-H, et al. Upregulation of miR-498 suppresses Th17 cell differentiation by targeting STAT3 in rheumatoid arthritis patients. Sheng li xue bao:[Acta physiologica Sinica]. 2018;70(2):167-74.

[95] Dai Y, Huang L, Zhang H, Hong G, He Y, Hu J, et al. Differentially expressed microRNAs as diagnostic biomarkers for infected tibial non-union. Injury. 2021;52(1):11-8.