Vol.6, No. 3, July 2021,
Webpage: http://rheumres.org
Email: rheumres@gmail.com
ISSN:2476-5856
doi: 10.32592/RR.2021.6.3.123


Review Article Open Access

# miRNAs and rheumatoid arthritis: new update in expression pattern and pathogenicity

**Hamidreza Ebrahimiyan[1,2] Arman Ahmadzadeh[3]***

*1.Department of Stem Cells and Developmental Biology, Cell Science Research Center, Royan Institute for Stem Cell Biology and Technology, ACECR, Tehran, Iran2.Rheumatology Research Center, Tehran University of Medical Sciences, Tehran, Iran3. Department of Adult Rheumatology, Loghman Hakim Hospital, ShahidBeheshti University of Medical Sciences, Tehran, Iran*

Rheumatoid arthritis (RA) is a polygenic autoimmune disease characterized by systemic inflammation and disability of joints. Early diagnosis and treatment could prevent diseases in RA patients from becoming severe. miRNAs are small, non-coding RNA that regulate the post-transcriptional level of gene expression. miRNAs play important roles in gene expression and pathogenicity of autoimmune diseases as well as RA. Properly using miRNAs regulation potential and detecting different expression patterns and their functions could facilitate and manage effective therapeuticinterventions in RA patients. Herein, we discuss miRNAs as a therapeutic agent in RA patients.

***Keywords:*** Rheumatoid arthritis (RA); miRNA; Expression, Regulation

## Introduction

Rheumatoid arthritis (RA) is a chronic autoimmune disease with systemic inflammation and multiple joint destructions. Like most other autoimmune diseases, RA is seen most frequently inwomen and older individuals [1, 2]. The synovial joints are the most important tissue in RA patients. Irreversible joint damage is seen in RA joints characterized by leukocyte infiltration and chronic inflammation [3, 4]. Beside immune cells function in RA joint inflammation, rheumatoid arthritis synovial fibroblasts (RASFs) are important cells in RA pathogenesis and are reported to be major effectors in joint inflammation and destruction [5-7].

Multiple factors are included in the RA pathogenicity, including various genes and environmental factors which trigger the autoimmune condition. Epigenetic variations are other important factors involved in RA pathogenicity [8]. Evidence has revealed the importance of miRNAs in gene expression and the development of autoimmune diseases like RA [9-14]. The association between miRNAs and RA was reported in 2008 when a significantly different expression pattern was observed in patients [15]. Several studies have reported the dysregulation of miRNAs in inflamed joints and peripheral blood of RA patients. The miRNAs have complete stability in body fluids, because this microenvironment has complexes with proteins that prevent degradation [16]. These molecules could be proper candidates for RA monitoring and treatment factors. Herein, we summarize and update the existing data on miRNA expression patterns, their potential validated targets, and pathologic factors in treatment interventions.

## miRNAs biogenesis and function

miRNAs are characterized as single-strand and small non-coding RNAs. Their mature forms are common negative regulators of gene expression by repressing translation or cleavage of mRNAs,although in some conditions, these molecules can be positive regulators


*Corresponding Author: Department of Adult Rheumatology, Loghman Hakim Hospital, ShahidBeheshti University of Medical Sciences, Tehran, Iran, E-mail: arman319@yahoo.com
**Received**:27 October 2020; **Accepted**:08 January 2021

of gene expression [17]. miRNA genes comprise only 1-2% of the whole genome, but they regulate around 30% of the protein encoded gene\s expression and 60% of genes have miRNA binding sites[17, 18]. Each miRNA molecule can have different functions in the case of multiple mRNAs or even in different transcripts of a single genes and generates miRNAs are important regulatory machines in various cells [17]. The biogenesis of miRNAsconsists of two different steps in the nucleus and cytoplasm. In the nucleus, the RNA polymerase II transcribes miRNA genes and generates a long primary transcript called primary miRNA (pri-miRNA). Each of these transcripts can be part of various mature miRNAs. The multiprotein complex including DGCR8 (DiGeorge syndrome critical region 8) as an RNA binding protein and Drosha as an endonuclease changes the pri-miRNA to precursor miRNA (pre-miRNA) in the nucleus. Pre-miRNAs are recognized by exportin-5 and transported to the cytoplasm. The other protein complex in the cytoplasm, RNA-induced silencing complex (RISC) which consists of RNase III (Dicer) and rgonaute (Ago), cleaves the pre-miRNA and generates a 19-22 nt asymmetric miRNA duplex. The active strand incorporates RISC and generates aribonucleoprotein complex that could target and degrade specific mRNAs [18]. The mature miRNA in the RISC complex can bind to a complementary sequence in 3'-UTR of mRNA. The degree of thecomplementarity is important in miRNA silencing function. In the case of complete binding, the other member of RISC which is named Ago mediates the regulatory function. The deadenylation or degradation of mRNA by the RISC complex represses gene expression [17, 18].

**Deregulated expression of miRNA in RA**

In Table 1, the different expression patterns of miRNAs in RA patients are classified based on their evaluation media or cells and including whole blood, synovial fluid, plasma, PBMCs, synovial tissue and RASFs in RA patients.

## Role of miRNAs in RA pathogenesis

In Table 2, some of the important roles of miRNAs are summarized based on immune cell function. The miRNAs are classified based on their function in TCR signaling, Th17 and Treg cell differentiation, regulation of B cell and of fibroblast activation.

**Let-7a**

Let-7a targeted Kirsten rat sarcoma virus gene (K-Ras), extracellular signal-regulated kinase 1/2 (ERK1/2), and c-Jun N-terminal kinase (JNK) increase the pro-inflammatory cytokines such as interleukin 1β (IL-1β) and may play important roles in RA pathogenesis. The downregulation of Let-7a in RA patients may be important in inducing pro-inflammatory cytokine expression [19].

**miR-10a**

One important miRNA in RA pathogenesis could be miR-10a, which was reported to increase the expression of inflammatory mediators such as IL-6, IL-8, TNF, IL-1, MCP1, matrix metalloproteinase1 (MMP1), and MMP13, which are important in RA development [20]. miR-10a also regulates the differentiation of TH17 cells that are important in RA development [21, 22].

**miR-15a, miR-16**

miR-16 is positively correlated with disease activity and determined by erythrocyte sedimentation rate (ESR), tender joint count (TJC), C-reactive protein (CRP), and the disease-activity-score-of-28-joints (DAS28) index [23, 24]. One of the important pro-inflammatory factors is tumor necrosis factor-α (TNF-α), which is targeted by miR-16 and can be a regulatory mechanism of inflammation in RA [23]. It was recently reported that low expression levels of miR-15a and miR-16 resulted in the upregulation of their target, SRY-Box Transcription Factor 5 (SOX5), which induced cell migration, invasion, and IL-1β and TNFα expression in RASFs [25].

**miR-17~92 cluster**

This cluster encoded 6 distinct members: miR17, 18a, 19a, 19b, 20a, and 92a. miR-17 upregulation in serum exosome was correlated with a decreased Treg proportion in RA patients [26]. The disturbed expression level of miR17~92 cluster altered the analogy of different subsets of T γδ cells in RA patients [27]. Other evidence revealed that miR-17 acts as a negative regulator of TNF-α by targeting TNF receptor-associated factor 2 (TRAF2) in RASFs, repressing the production of IL-6, IL-8, MMP-1, and MMP-13 in these cells. The downregulation of miR-17 in RASFs resulted in the promotion of inflammation in RA joints [28].

The other member of the cluster, upregulated miR-18a, increased inflammation by targeting tumor necrosis factor-alpha-induced protein 3 (TNFAIP-3), a negative regulator of NF-κβ signaling and protein inhibitor of activated STAT-3 (PIAS-3) that suppressed the STAT-3 signaling pathway. miR-18a induced the expression of inflammatory mediators such as IL-6, IL8, MCP, and MMP1 and regulated the activation of normal T cells[29].

It has been reported that miR-19a/b regulates the expression of TLR2 in RASFs, which reduces inflammation by decreasing IL-6 and MMP-3 [30].

The suppression of cytokine signaling 3 (SOCS3) was reported to be another important target of miR-19a-3p, which was upregulated in response to the low expression levels of miR-19a-3p which inhibited proliferation and induced apoptosis in RASFs [31]. miR-20, another member of the miR-17~92 cluster, also exhibits anti-inflammatory properties. It has been reported to control pro-inflammatory cytokine production by RASFs. miR-20-dependent apoptosis signal-regulating kinase 1 (ASK1) repression decreases the production of IL-6 and MMP-3 [30, 32]. The important roles of ASK1 in RA development and pro–inflammatory cytokine production have been reported in different animal models [33, 34]. A disintegrin and metalloproteinase domain‑ containing protein 10 (ADAM10) is another target of miR-20a, and the downregulation of miR-20a results in cell viability, migration and invasion, and the expression of inflammatory cytokines in RASFs [35].

**miR-21**

Lower levels of miR-21expression were correlated with increased ratios of T-helper 17 (Th17) to regulatory T cells (Treg). miR-21 may also be correlated with increased expression of signal transducer and activator of transcription 3 (STAT3), an important transcription for Th17 differentiation. miR-21 has a high expression level in Tregs compared to conventional T cells and is important for Th17 differentiation [36]. In another study, the upregulation of miR-21 was reported to be associated with a significant increase in NF-κβ levels and cell proliferation in RASFs [37].

**miR-22, miR-23b and miR-30a**

Lower expression levels of miR-22 were correlated with increased expression of cysteine-rich angiogenic inducer 61 (CYR61) as a direct target gene. CYR61 is an extracellular matrix protein produced by RASFs and stimulates these cell expansions and IL-6 production, which is an important factor in inflammation and Th17 differentiation [38]. miR-22 also targets Sirtuin 1 (SIRT1) in RASFs, and a decrease in miR-22 results in cell proliferation and the release of inflammatory cytokines, including TNF-α, IL-1β, and IL-6 [39]. IL-6R is also a target of miR-22 and plays important roles in the Nuclear factor kappa B (NF-κB) signaling pathway [40].

miR-23b regulates the expression of TNF-α, IL-17, and IL-1β by targeting TGF-β-activated kinase 1/ MAP3K7 binding protein 2 (TAB2), TAB3, and inhibiting nuclear factor κ-B kinase subunit α (IKK-α) in RASFs. Downregulated miR-23b, which increases the expression of these cytokines,may be important in the pathogenesis of RA [41].

Lower expression levels of miR-30a were associated with increased expression of Beclin-1 (BECN-1) and reduced apoptosis in RA synovium[42].

**miR-24**

miR-24 is positively correlated with CRP, DAS28, the visual analog scale of general health (VAS), and disease activity. It can increase the inflammatory response by targeting the expression of the furin enzyme, which is important in transforming growth factor-beta 1(TGF-β1) processing and peripheral tolerance maintenance [43].

**miR-26a**

miR-26a may be correlated with Th-17 differentiation, which is important in RA pathogenesis [44]. It has recently been reported that the overexpression of miR-26a-5p activates phosphoinositide 3-kinase (PI3K)/ protein kinase B, PKB (AKT) by targeting phosphatase and tensin homolog (PTEN) in RASFs. Overexpression of miR- 26a-5p induces proliferation, G1/S transition, invasion, and apoptosis resistance in RASFs [45].

**miR-27a**

The downregulation of miR-27a in RASFs results in the overexpression of follistatin-like protein 1 (FSTL1) which has been suggested to play a key role in RA development. This miRNA can repress important mediators such as MMP2, MMP9, and MMP13, and Rho family proteins (Rac1, CDC42, and RhoA). The expression of TLR4 and NF-κB is also inhibited by miR-27a in RASFs,as it inhibits the cell migration and invasion of RASFs which are important in RA pathogenicity [46].

**miR-29a**

Low expression levels of miR-29a in RASFs, which target STAT3, results in greater proliferation and apoptosis resistance [47].

**miR-30a-3p**

miR-30a-3p targets B cell-activating factor (BAFF) in RASFs, which results in decreased synthesis and release from these cells. Low expression levels of miR-30a-3p result in more BAFF release as well as B cell survival and autoimmune response in RA patients [48].

**miR-34a, miR-34b**

The hypermethylation of miR-34a promoter leads to the downregulation of miR-34a in RASFs in RA patients. The X-linked inhibitor of apoptosis protein (XIAP),which has been known to be an important direct target of miR-34a, is upregulated in RASFs. Decreased expression of this miRNA is associated with prolonged cellular lifespan and more inflammation and destruction in the joints of RA patients [49]. It has recently been reported that miR- 34a can also target cyclin I to activate the ATM/ataxia telangiectasia and Rad3-related (ATR)/p53 signaling pathway and inhibit

RASF proliferation and inflammation in RA joints [50]. Another recent study has revealed that miR-34a-5p targets X-box binding protein 1 (XBP1). Increased expression of XBP1 results in proliferation and overproduction of TNF-α and IL-6 in RASFs [51]. Murine double minute 4 (MDM4) is another target of miR‑ 34a‑ 3p in RASFs. Low expression levels of miR‑ 34a‑ 3p are correlated with the upregulation of cyclin-dependent kinase 2 (CDK2), cell division cycle 25A (CDC25A), and cyclin D1 which induce proliferation and are correlated with the induced production of MMP-1, MMP-9, and pro-inflammatory cytokines such as TNF-α and IL-6 in RASFs [52]. The decreased expression of the cAMP response element-binding proteins (CREBs) is correlated with dysfunction in RASFs and RA pathogenesis [53]. CREBsare a direct target of miR-34b and may be associated with RA disease activity [54].

**miR-101**

Inducible T-cell co-stimulator (ICOS)-deficient mice are resistant to collagen-induced arthritis. The ICOS is one of the best targets of miR-101 and might be a therapeutic candidate for RA [55]. Downregulation of miR101-3p in RASFs results in the overexpression of prostaglandin-endoperoxide synthase 2 (PTGS2), which induces cell proliferation, migration, and invasion and attenuates apoptosis [56, 57].

**miR-103a**

A previous study has shown that miR-103a upregulation is correlated with the downregulation of DICER1, argonaute RISC component 1(AGO1), cAMP responsive element-binding protein 1(CREB1), death-associated protein kinase 1 (DAPK1), and P53; the exact role of this miRNA, however, remains to be clarified [58].

**miR-124a**

Increased expansion of RASFs may be associated with the lower expression of miR-124a. Overexpression of miR-124a leads to the inhibition of monocyte chemoattractant protein-1 (MCP-1), CDK-2, and vascular endothelial growth factor (VEGF) expression, resulting in decreased angiogenesis and inflammation and more apoptosis in RASFs [59]. Thus, a low level of miR-124a results in the overexpression of MCP-1, also known as chemokine (C-C motif) receptor 2 (CCR2), and the recruitment of monocytes into inflamed joints. Moreover, it has been reported that phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha (PIK3CA) is one of the direct target genes for miR-124a. It is not surprising that lower miR-124a expression contributes to the activation of the PIK3/Akt/NF-κβ signaling pathway and induces the production of pro-inflammatory factors like TNF-α and IL-6 in RASFs [60].

**miR-99a/miR-100/miR-125b, miR125a**

miR-125b is co-expressed with miR-99 and miR-100. miR-125b and miR125a have been reported to activate the NF-κB signaling pathway which is involved in the production of pro-inflammatory cytokines, and they may initiate the inflammation response in RA joints [61].

**miR-126-3p**

In 2012, Wang et al. reported the decreased expression of miR-126-3p in RA plasma; however, a 2013 study reported markedly elevated miR-126-3p levels in RA plasma [43, 62]. Recently, the downregulation of miR-126 in RASFs has been reported, which results in the upregulation of IL-23R, TNF-α, and IFN-γ in these cells [63]. However, another study has revealed that miR-126 overexpression in RASFs targets phosphoinositide-3-kinase regulatory subunit 2 (PIK3R2) expression and promotes proliferation while inhibiting apoptosis [64,65].

**miR-128-3p**

miR-128-3p targets histone deacetylase 4 (HDAC4) in RASFs. miR-128-3p/HDAC4 axis regulates RA development through AKT/mTOR pathway. miR-128-3p upregulation results in more proliferation, migration, invasion, inflammation, and apoptosis resistance in RASFs [66].

**miR-132**

The expression of miR-132 is increased in PBMCs; however, the monocyte fraction of RA expresses more than threefold expression of miR-132 compared to the lymphocyte fraction [23]. The plasma level is decreased and correlates inversely with TJC and is possibly a consequence of inflammation in RA [24].

**miR-137**

miR-137 targets the C-X-C motif chemokine ligand 12/ stromal cell-derived factor 1 (CXCL12/ SDF1) in RASFs, resulting in reductionsinthe proliferation, invasion, migration, and expression of inflammatory cytokines from RASFs [67].

**miR-140-3p, miR-140-5p**

Lower expression levels of miR140-3p and miR-140-5p in RASFs increase proliferation responses, migration, and cytokine production abilities, while they decrease apoptosis. miR-140-3p and miR-140-5p target SIRT1 and stromal cell-derived factor 1 (SCDF1) in RASFs [68]. Recently, STAT3 was reported to be the target of miR140-5p in RASFs [69].

**miR-133a, miR-142-3p, miR-142-5p**

The miR-142 expression level was ten times more than that of miR-133 in RASFs. The runt-related transcription factor 2 (Runx2), which is essential for

osteoblast differentiation, is a target of miR-133 [70]. This gene is also a suppressor of cell division control protein 42 (CDC42) and is involved in cellular differentiation and cell cycle progression [71]. Downregulation of miR-142-3p inhibits the aggressive phenotypes of RASFs by inhibiting the NF-κB signaling pathway. miR-142-3p targets interleukin-1 receptor-associated kinase 1 (IRAK1) in RASFs and is correlated to the upregulation of IL-6, MMP-3, and B cell lymphoma 2 (Bcl-2) as well as the downregulation of BCL2 associated x, apoptosis regulator (Bax), and BCL2 associated agonist of cell death (Bad), which reduce apoptosis and promote proliferation and inflammation in RASFs [72].

**miR-143**

miR-143 targets insulin-like growth factor binding protein 5 (IGFBP5) in RASFs. Upregulated miR-143 results in IGFBP5 deficiency that increases the sensitivity of RASFs to TNFα stimulation and promotes IL-6 and NF-κβ activity in these cells [73]. miR-143-3p can also target insulin-like growth factor 1 receptor (IGF1R) in RASFs. Moreover, it increases cell proliferation and reduces apoptosis by targeting these genes and promotes Ras/p38 mitogen-activated protein kinase (MAPK) signaling pathways [74]. TNF alpha-induced protein 3 (TNFAIP3) is the target of miR-143-3p and is downregulated in RASFs, which leads to induced proliferation, inflammation, and attenuated apoptosis [75].

**miR-145**

miR-145 targets semaphorin 3A (SEMA3A) in RASFs. miR-145 overexpression results in more susceptibility to vascular endothelial growth factor (VEGF) that increases the survival, migration, and invasion of RASFs [73]. miR-145-5p aggravates RA development by promoting the NF-κB pathway, which enhances secretion of MMP-3, MMP-9, and MMP-13 in RASFs [76].

**miR-146a, miR-146b**

miR-146a is one of the most studied miRNAs in RA patients. Increased expression of miR-146a was detected in various cells such as T cells, B cells, monocytes, and IL-17-producing CD4+ cells [15, 23, 44, 77-79]. However, decreased expression in plasma of RA patients was reported in some studies [62, 80]. miR-146a inhibits the TH1 mediated response and requires Treg (regulatory) activity, which is importantin RA inflammation [81, 82]. Overexpression of miR- 146a suppresses T cell apoptosis by regulating Fas-associated factor 1, which is important in cellular apoptosis [77]. Different studies have reported conflicting evidence regarding the role of miR-146a in RA pathogenesis. Some have reported a positive correlation between miR-146a and disease indices like CRP, ESR, DAS28, and plasma ; however, others have reported no correlation or inverse correlation with TJC [23, 24, 77, 79]. miR-146b is positively correlated with IL-17 producing lymphocytes and enabling the infiltration of these pathogenic cells to the synovium[44]. Both of these miRNAs regulate various essential genes in apoptosis and inflammation and could be linked to RA pathogenesis [23, 77, 78]. miR-146a levels were upregulated in RASFs after IL-1β and lipo-polysaccharide (LPS) stimulation [15]. Promotor analysis revealed that NF-κB, an essential transcription factor in response to pro-inflammatory cytokines, induced the expression of miR-146a under conditions of inflammation [83]. The TNF receptor-associated factor 6 (TRAF6) and IRAK1 were two target genes of miR-146a; however, the upregulated miR-146a did not change the expression pattern of these genes in RA patients. Under normal conditions, upregulated miR-146a can inhibit the expression of TRAF6 and IRAK1, which in turn results in the downregulation of TNF-α.In RA conditions, however, it seems that upregulated miR-146a is not sufficient to control TNF-α expression [23, 83]. Some other putative targets, including interferon regulatory factor-5 (IRF5) and signal transducer and activator of transcription-1 (STAT1) which are involved in type I IFN signaling pathway and Fas-associated factor-1 (FAF1), Fas-associated death domain proteins (FADD) which are involved in activation-induced cell death (AICD), and FAS-mediated apoptosis in T cells, should be investigated to clarify better the miR-146a pathogenicity in RA inflammation [77, 83-85]. miR-146a could affect osteoclast differentiation by targeting the master genes of osteoclastogenesis, such as c-Jun, nuclear factor of activated T-cells, cytoplasmic 1 (NF-ATc1), PU.1, and tartrate-resistant acid phosphatase (TRAP) [83, 86, 87]. In CIA mice treated with miR-146a, a significant decrease in cartilage and bone destruction has been reported; however, inflammation has not been inhibited [88].

**miR-150**

High expression levels of miR-150 are correlated with IL-17 producing cells, disease activity, and joint destruction. miR-150 is also important in the differentiation of IL-17-producing cells, an important pathogenic factor in RA [44, 89, 90]. Another recent study has shown that miR-150 overexpression results in the downregulation of its target, SOCS1, which induces pro-inflammatory cytokine production and proliferation of RASFs [91].

**miR-152**

miR-152 targets ADAM10 in RASFs. Downregulation of miR-152 significantly increases cell proliferation,

TNF-α, IL-1β, IL-6, and IL-8 production and inhibits cell apoptosis in RASFs [92]. miR-152 also targets DNA methyltransferase (DNMT1), resulting in the inhibition of canonical Wnt signaling. Low expression levels of this miRNA in RASFs induce DNMT1 and Wnt signaling; however, upregulated DNMT1 induces miR-152 expression in these cells [93, 94].

**miR-155**

Based on previous studies, two opposite functions of miR-155 should be noticed in RA pathogenicity: detrimental involvement and protective involvement. Most studies have revealed the increased expression level of miR-155 in different cells such as RASFs, synovial fluid CD14+ cells, and synovium macrophages, which is correlated with the lower expression of important target genes such as Src homology 2-containing inositolphosphatase-1(SHIP-1), a potent inhibitor of inflammation that increases the risk of autoimmunity in patients [15, 95, 96]. Overexpression of miR-155 in CD14+ cells stimulates the production of pro-inflammatory cytokines including IL-1β, IL-6, IL-8 and TNF-α [95]. IL-10 is downregulated by miR-155 and can modulate miR-155 itself [95, 97]. Like miR-146a, miR-155 might regulate various signaling pathways, and it plays roles in RA pathogenicity [15, 95, 98]. miR-155 is required for Treg, TH1 and TH17 differentiation and function [44, 83, 95, 99]. miR-155 is involved in TH17 differentiation, antigen-driven B cell maturation, and differentiation of Ig class-switched cells [100, 101]. The level of miR-155 in RASFs is upregulated after pro-inflammatory cytokine stimulation such as IL-1β, TNF-α, or TLR ligands [15]. A recent study reported that miR-155 targets Janus Kinase (JAK2/STAT3) and inhibits IL6-mediated activation in RASFs [102]. It has also been recently reported that by targeting forkhead box protein O3a (FOXO3a), miR-155 promotes the secretion of inflammatory cytokines such as IL-1β, IL-6, and TNF-α and induces the proliferation of RASFs [103]. Some other target genes which might be important in RA inflammation include PU.1 and musculoaponeuroticfibrosarcoma(c-Maf), which are important in dendritic cell maturation and hematopoietic development FADD;IkB kinase (IKK) that is a positive regulator of NF-κB;and the receptor-interacting serine-threonine kinase 1 (RIPK1).These genes need to be investigated to clarify the roles of miR-155 in RA pathogenesis. By reducing cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) expression in CD4+ human T cells and promoting T cell-dependent tissue inflammation, miR-155 could enhance inflammation in RA joints [104, 105]. In miR-155 deficient mice, decreased systemic levels of IL-6 and IL-17 are seen after the induction of CIA; however,these mice do not develop either clinical or histologic signs of CIA [95, 106-108].

Some studies also have reported the protective function of miR-155 in RA patients. The overexpression of miR-155 reduces the expression of MMP-3 and impairs MMP-1 and MMP-3 induction by cytokine and TLR ligands in RASFs [15]. Downregulation of MMPs could alleviate tissue damage in inflamed joints. It is proposed that the microenvironment in RA synoviumupregulates miR-155 expression and controls feedback on the inflammatory response [95]. miR-155 is involved in Treg differentiation and maintaining its proliferative activity [100, 109].

**miR-181a**

miR-181a could potentially be important in RA pathogenicity. Any decreased or increased expression level affects the T cell maturation and selection process which increases the risk of autoimmunity. Downregulated miR-181a increases TCR sensitivity, while upregulated miR-181a increases the stimulation threshold of TCR. miR-181a also targets an important gene in T cell function called the protein tyrosine phosphatase non-receptor type 22 (PTPN22), which is important in RA pathogenicity [110-112].

**miR-188-5p**

miR-188-5p may target cell migration-inducing and hyaluronan-binding protein (CEMIP also named KIAA1199) and indirectly regulate collagen type I alpha (COL1A1 and COL12A1) expression in RASFs. Decreased miR-188-5p results in greater activation and migration of RASFs [113].

**miR-192**

Caveolin 1 (CAV1) is identified as a direct target of miR-192. Upregulated CAV1 results in increased cell proliferation and inhibition of apoptosis in RASFs. miR-192 is downregulated in RA synovial tissues, which elicits growth effects on RASFs by targeting CAV1 [114].

**miR-199a-3p**

miR-199a-3p targets retinoblastoma 1 (RB1) mRNA and suppresses its expression in RASFs. Reduced MiR-199a-3p in RASFs results in RB1upregulation which increases cellular proliferation and decreases apoptosis in these cells [115].

**miR-203**

Elevated expression of miR-203 stimulates the production of MMP-1 and the NF-κB-related production of IL-6, which is associated with activated RASFs and inflammation in RA joints [116]. A recent study revealed that HMG-box transcription factor 1 (HBP1) is a target of miR-203. HBP1 suppresses cell

proliferation and the production of inflammatory cytokines including IL-6, IL-1β, IL-8, and TNF-α, while it inhibits apoptosis in RASFs [117].

**miR-204, miR-211**

miR-204 and miR-211 target activating transcription factor 2 (ATF2) in RASFs. Downregulated miR-204 and miR-211 result in increased inflammation in RA joints [118]. It has recently been reported that miR-204-5p targets nuclear paraspeckle assembly transcript 1 (NEAT1) in RASFs. Upregulated NEAT1 in these cells induces the NF-κβ pathway and increases cellproliferationandinflammatory cytokine production while inhibiting cell apoptosis [119]. **miR-212-3p** The SOX5 gene is a target of miR-212-3p in RASFs. Decreased expression of miR-212-3p promotes cell growth and reduces cell apoptotic rates, which are important in RA pathogenesis [120].

**miR-218-5p**

RASFs have multilineage differentiation potential, including osteoblasts. miR-218-5p is overexpressed in the early phase of osteogenic differentiation and then decreased. miR-218-5p targets roundabout 1 (ROBO1) and indirectly decreases dickkopf-related protein 1 (DKK1) secretion, which promotes osteogenic differentiation [121].

**miR-221/miR-222**

miR-221 and miR-222 are co-expressed and target the same genes. Overexpression of these miRNAs could enhance the production of pro-inflammatory cytokines, promote the activation and migration of RASFs, and prolong the cellular lifetime through apoptosis resistance [122]. miR-221 targets DKK2 and bone morphogenetic proteins (BMPs), resulting in decreased mineralization, apoptosis, and osteoblastogenesis and pro-inflammatory cytokines production in RASFs [96, 122, 123].

**miR-223**

miR-223 regulates the differentiation of osteoclasts and has important roles in the state of RA joints[124]. Overexpression of miR-223 could suppress the production of cathepsin K as well as osteoclast-related genes, and it has a function in the renewal of bone and osteoclastogenesis [124]. One of its important target genes is neurofibromatosis type 1 (NF-1A), which is repressed and results in osteoclast differentiation [125]. The main sources of high concentrations of miR-223 in inflammation sites seem to be macrophages, monocytes, CD4+ T cells, RASFs, and peripheral T cells [24, 59, 124, 126]. However, the expression level of miR-223 might have no correlation with DAS28, CRP, anti-citrullinated peptide antibody (ACPAs), or disease duration; have a strong correlation with rheumatoid factor (RF); and have a negative correlation with TJC index [24, 54, 126, 127]. CIA mice treated with miR-223 showed decreased arthritis scores and no pannus formation [128]. miR-223 also targets IL-17RD in RASFs and contributes to the pathogenesis of RA by downregulating the expression of IL-17RD and increasing the production of IL-6 in these cells [129]. It also targets the NLR family pyrin domain containing 3 (NLRP3). Upregulated NLRP3 induces proliferation and inflammatory cytokine secretion and attenuates apoptosis in RASFs [130].

**miR-301a-3p**

The expression of RAR-related orphan receptor gamma (RORγt) and STAT3 is increased in the PBMCs of RA patients, which is correlated with increased TH17 frequency and pro-inflammatory cytokines. miR-301a-3p targets the protein inhibitor of activated STAT3 (PIAS3), the main cellular inhibitor of STAT3, and downregulated miR-301a-3p, resulting in more expression of STAT3 in RA patients [131].

**miR-320a**

Low expression levels of miR-320a correlate with decreased Bax/Bcl-2 ratios, which inhibits apoptosis in RASFs. miR-320a expression levels also correlate with MAPK ERK1/2 signaling pathways[132].

**miR-323-3p**

The higher expression level of miR-323-3p in RASFs inhibits its target genes, including BTRC (β-transducin repeat containing E3 ubiquitin-protein ligase) and β-catenin inhibitor, and enhances theWnt/cadherin signaling pathway. The increase in Wnt/cadherin signaling and upregulation of β-catenin have been described as important factors in the activation and function of RASFs[96, 133].

**miR-338-5p**

The nuclear factor of activated T-cells 5 (NFAT5) is a target of miR-338-5p in RASFs. Overexpressed miR-338-5p increases the proliferation, migration, and invasion of these cells which are important in RA pathogenesis [134].

**miR-340-5p**

miR-340-5p targets STAT3 in RASFs. Downregulated miR-340-5p results in increased proliferation and decreased apoptosis in these cells [135].

**miR-346**

miR-346 is upregulated after LPS treatment in RASFs. Suppression of miR-346 results in IL-18 release and might have a regulatory function in inflamed joints [136]. miR-346 targets Bruton's tyrosine kinase (BTK) and tristetraprolin (TTP), resulting in TNF-α expression and more inflammation by RASFs [137].

**miR-363, miR-498**

miR-363 and miR-498 are decreased in the CD4+ T cells of RA patients [77]. These miRNAs are elevated in RA peripheral blood or synovial fluid, but their role

in RA pathogenesis remains unclear [77].

**miR-375**

miR-375 plays a critical role in the promotion of the canonical Wnt signaling pathway by targeting the Frizzled 8 (FZD8). The decreased expression level of miR-375 results in inflammation and plays a pathogenic role in RA development [138]. It has recently been reported that miR-375 targets TAK1-binding 2 (TAB2) in RASFs. TAB2 enhances cell cycle, proliferation and inflammatory response while inhibiting apoptosis in RASFs [139].

**miR-410-3p**

Downregulated miR-410-3p correlates with the production of pro-inflammatory cytokines including TNF-α, IL-1β, IL-6, and MMP-9 by regulating the NF-κβ signaling pathway in RASFs [140]. It has been verified that miR-410-3p regulates inflammation by targeting Yin Yang 1 (YY1) in these cells [141].

**miR-451**

Increased expression of miR-451 has been reported in RA peripheral blood T cells, but its downregulation has also been reported in RA neutrophils [62, 99, 142]. Suppression of miR-451 in neutrophils could enhance chemotaxis by p38 MAPK [142]. The level of miR-451 has been decreased in T cells after treatment compared to active RA patients [99]. miR-451 is also positively correlated with DAS28, ESR, and IL-6 concentrations in serum [99].

**miR-483-3p**

miR-483-3p targets IGF1 which is important in RA pathogenesis. Upregulated miR-483-3p results induced proliferation, the G0/G1-to-S phase transition, and attenuated apoptosis in RASFs [143].

**miR-495**

Decreased expression of miR-495 in RASFs results in the upregulation of β-catenin, MMP-2, MMP-9, IL-6,IL-11, and TNF-α and induces proliferation in these cells [144].

**miR-506**

The downregulation of miR-506 results in attenuated apoptosis along with a decrease in the activities of cysteine-aspartic proteases, cysteine aspartases, and cysteine-dependent aspartate-directed proteases (caspase-3 and -8). Toll-like receptor 4 (TLR4) is an important target of miR-506 in RASFs. Enhanced expression of TLR4 inhibits apoptosis and induces proliferation in these cells [145].

**miR-522**

The over expression of miR-522 increases the expre-ession levels of TNF-α, IL-1β and MMP-1, MMP-3, and MMP-13 by targeting SOCS3 in RASFs [146].

**miR-539**

miR-539 targets osteopontin (OPN) in RASFs. Decreased levels of miR-539 result in an increased level of OPN in the blood and synovial fluid of RA patients that promotes cellular proliferation in RA joints [147].

**miR-548a-3p**

Serum exosomal miR-548a-3p is downregulated and associated with high levels of CRP, RF, and ESR in the serum of RA patients. miR-548a-3p targets the TLR4/NF-κB signaling pathway. Low expression levels of miR-548a-3p increase NF-κβ-mediated inflammation and might promote proliferation and activation of inflamed cells in RA patients [148].

**miR-573**

miR-573 has been introduced as an anti-inflammatory miRNA which represses the expression of thioredoxin domain-containing 5 (TXNDC5) in the synovial tissue of RA patients, which in turn regulates MMP-3 expression. It also decreases the expression of IL-6 and COX2 in RA patients. miR-573 can target TLR2 and EGFR, which reduce the inflammation and angiogenesis in synovial tissue. Moreover, it attenuates different signaling pathways, including PI3K/Akt, ERK1/2, MAPK, and STAT3, in response to lipopolysaccharides (LPS) [149, 150].

**miR-613**

DKK1 is a target of miR-613 in RASFs. Enhanced DKK1 in RASFs induces cellular proliferation, and invasion and decreases apoptosis in these cells [151].

**miR-650**

miR-650 targets RAC-beta serine/threonine-protein kinase (AKT2) in RASFs. Downregulation of miR-650 results in the upregulation of AKT2 which increases the proliferation, migration, and invasion of RASFs and decreases apoptosis in these cells [152]. It has recently been shown that miR-650 targets 2',3'-cyclic nucleotide 3'-phosphodiesterase (CNP). Upregulated CNP promotes cell proliferation, inflammatory response, invasion, migration, and suppressed apoptosis in RASFs [153].

**miR-663**

miR-663 targets the adenomatous polyposis coli (APC) which triggers the canonical Wnt signaling through the accumulation of β-catenin in RASFs. Increased miR-663 enhances cellular proliferation and the production of MMP3 and fibronectin in RASFs [154].

## Conclusion

Unraveling the etiology of autoimmune diseases remains a big challenge in the field of immunology and genetics. In recent years, miRNAs have been important research objects in various laboratories.

miRNAs play a multi-faceted role in the development of RA and are part of an extensive complex network Unraveling the etiology of autoimmune diseases remains a big challenge in the field of immunology and genetics. In recent years, miRNAs have been important research objects in various laboratories. miRNAs play a multi-faceted role in the development of RA and are part of an extensive complex network in autoimmunity. A plethora of miRNA alterations in different cells affect pathophysiology and the disease process. Furthermore, the exact expression pattern of various miRNAs in only a single cell and, more importantly, their interaction and different target genes by only one miRNA are still not entirely understood. However, different miRNAs target genes could be a completely complex network in the development and pathology of RA. Each miRNA and its expression pattern could be a potential target of therapeutic agents, but this could also be a double-edged sword and induce more inflammation in already-inflamed joints.

The identification of miRNAs as therapeutic agents involves other issues, including multiple regulators for a single mRNA, the synergistic or antagonistic activity of other miRNAs, and the participation of various regulators of gene expression such as genetic or epigenetic agents.

**Acknowledgement**

Not applicable.

**Conflicts of Interest**

The authors declare that they have no conflicts of interest.

**Funding**

No funds.

## References

1. Uhlig T, Moe RH, Kvien TK. The burden of disease in rheumatoid arthritis. ***Pharmacoeconomics***2014; 32(9):841-51. doi: 10.1007/s40273-014-0174-6.
2. Rossini M, Rossi E, Bernardi D, Viapiana O, Gatti D, Idolazzi L. *et al*. Prevalence and incidence of rheumatoid arthritis in Italy. ***Rheumatol Int***2014; 34(5):659-64. doi: 10.1007/s00296-014-2974-6.
3. Müller-Ladner U, Pap T, Gay RE, Neidhart M, Gay S. Mechanisms of disease: the molecular and cellular basis of joint destruction in rheumatoid arthritis. ***Nat Clin Pract Rheumatol*** 2005; 1(2):102-10. doi: 10.1038/ ncprheum0047.
4. Feldmann M, Maini RN. Anti-TNFα therapy of rheumatoid arthritis: what have we learned? ***Annu Rev Immunol*** 2001; 19(1):163-96. doi: 10.1146/ annurev.immunol.19.1.163.
5. Rockel JS, Kapoor M. Erratum: Autophagy: controlling cell fate in rheumatic diseases. ***Nat Rev Rheumatol*** 2017; 13(3):193-93. doi: 10.1038/nrrheum.2017.17.
6. Qin B, Yang M, Fu H, Ma N, Wei T, Tang Q. *et al*. Body mass index and the risk of rheumatoid arthritis: a systematic review and dose-response meta-analysis. ***Arthritis Res Ther*** 2015; 17(1):86. doi: 10.1186/s13075-015-0601-x.
7. Bartok B, Hammaker D, Firestein GS. Phosphoinositide 3-kinase δ regulates migration and invasion of synoviocytes in rheumatoid arthritis. ***J Immunol*** 2014; 192(5):2063-70. doi: 10.4049/jimmunol.1300950.
8. Vojdani A. A potential link between environmental triggers and autoimmunity. ***Autoimmune Dis***2014; 2014:437231. doi: 10.1155/2014/437231.
9. Thamilarasan M, Koczan D, Hecker M, Paap B, Zettl UK. MicroRNAs in multiple sclerosis and experimental autoimmune encephalomyelitis. ***Autoimmun Rev*** 2012; 11(3):174-79. doi: 10.1016/j.autrev.2011.05.009.
10. Singh RP, Massachi I, Manickavel S, Singh S, Rao NP, Hasan S. *et al*. The role of miRNA in inflammation and autoimmunity. ***Autoimmun Rev***2013; 12(12):1160-65. doi: 10.1016/j.autrev.2013.07.003.
11. Salehi E, Eftekhari R, Oraei M, Gharib A, Bidad K. MicroRNAs in rheumatoid arthritis. ***Clin Rheumatol*** 2015; 34(4):615-28. doi: 10.1007/s10067- 015-2898-x.
12. Jimenez SA, Piera-Velazquez S. Potential role of human-specific genes, human-specific microRNAs and human-specific non-coding regulatory RNAs in the pathogenesis of Systemic Sclerosis and Sjögren's Syndrome. ***Autoimmun Rev*** 2013; 12(11):1046-51. doi: 10.1016/j.autrev.2013.04.004.
13. Iborra M, Bernuzzi F, Invernizzi P, Danese S. MicroRNAs in autoimmunity and inflammatory bowel disease: crucial regulators in immune response. ***Autoimmun Rev*** 2012; 11(5):305-14. doi: 10.1016/ j. autrev.2010.07.002.
14. Chatzikyriakidou A, Voulgari PV, Georgiou I, Drosos AA. miRNAs and related polymorphisms in rheumatoid arthritis susceptibility. ***Autoimmun Rev*** 2012; 11(9):636-41. doi: 10.1016/j.autrev.2011.11.004.
15. Stanczyk J, Pedrioli DML, Brentano F, Sanchez-Pernaute O, Kolling C, Gay RE. *et al*. Altered expression of MicroRNA in synovial fibroblasts and synovial tissue in rheumatoid arthritis. ***Arthritis Rheum*** 2008; 58(4):1001-09. doi: 10.1002/art.23386.
16. Gibbings DJ, Ciaudo C, Erhardt M, Voinnet O. Multivesicular bodies associate with components of miRNA effector complexes and modulate miRNA activity. ***Nat Cell Biol*** 2009; 11(9):1143-49. doi: 10.1038/ ncb1929.
17. Furer V, Greenberg JD, Attur M, Abramson SB, Pillinger MH. The role of microRNA in rheumatoid arthritis and other autoimmune diseases. ***Clin Immunol*** 2010; 136(1):1-15. doi: 10.1016/j.clim.2010.02.005.
18. Ha M, Kim VN. Regulation of microRNA biogenesis. ***Nat Rev Mol Cell Biol*** 2014; 15(8):509-24. doi: 10.1038/ nrm3838.
19. Lai NS, Yu HC, Yu CL, Koo M, Huang HB, Lu MC. Anti-citrullinated protein antibodies suppress let-7a

expression in monocytes from patients with rheumatoid arthritis and facilitate the inflammatory responses in rheumatoid arthritis. ***Immunobiology*** 2015; 220(12):1351-58. doi: 10.1016/j.imbio.2015.07.007.

20. Mu N, Gu J, Huang T, Zhang C, Shu Z, Li M. *et al*. A novel NF-κB/YY1/microRNA-10a regulatory circuit in fibroblast-like synoviocytes regulates inflammation in rheumatoid arthritis. ***Sci Rep*** 2016; 6(1):20059. doi: 10.1038/srep20059.
21. Wu W, He C, Liu C, Cao AT, Xue X, Evans-Marin HL. *et al*. miR-10a inhibits dendritic cell activation and Th1/Th17 cell immune responses in IBD. ***Gut***2015; 64(11):1755-64. doi: 10.1136/gutjnl-2014-307980.
22. Takahashi H, Kanno T, Nakayamada S, Hirahara K, Sciumè G, Muljo SA. *et al*. TGF-β and retinoic acid induce the microRNA miR-10a, which targets Bcl-6 and constrains the plasticity of helper T cells. ***Nat Immunol***2012; 13(6):587-95. doi: 10.1038/ni.2286.
23. Pauley KM, Satoh M, Chan AL, Bubb MR, Reeves WH, Chan EK. Upregulated miR-146a expression in peripheral blood mononuclear cells from rheumatoid arthritis patients. ***Arthritis Res Ther***2008; 10(4):R101. doi: 10.1186/ar2493.
24. Murata K, Yoshitomi H, Tanida S, Ishikawa M, Nishitani K, Ito H. *et al*. Plasma and synovial fluid microRNAs as potential biomarkers of rheumatoid arthritis and osteoarthritis. ***Arthritis Res Ther***2010; 12(3):R86. doi: 10.1186/ar3013.
25. Wei H, Wu Q, Shi Y, Luo A, Lin S, Feng X. *et al*. MicroRNA-15a/16/SOX5 axis promotes migration, invasion and inflammatory response in rheumatoid arthritis fibroblast-like synoviocytes. ***Aging (Albany NY)***2020; 12(14):14376-90. doi: 10.18632/aging.103480.
26. Wang L, Wang C, Jia X, Yu J. Circulating exosomal miR-17 inhibits the induction of regulatory T cells via suppressing TGFBR II expression in rheumatoid arthritis. ***Cell Physiol Biochem***2018; 50(5):1754-63. doi: 10.1159/000494793.
27. Guggino G, Orlando V, Saieva L, Ruscitti P, Cipriani P, La Manna MP. *et al*. Downregulation of miRNA17–92 cluster marks Vγ9Vδ2 T cells from patients with rheumatoid arthritis. ***Arthritis Res Ther***2018; 20(1):236. doi: 10.1186/s13075-018-1740-7.
28. Akhtar N, Singh AK, Ahmed S. MicroRNA-17 Suppresses TNF-α Signaling by Interfering with TRAF2 and cIAP2 Association in Rheumatoid Arthritis Synovial Fibroblasts. ***J Immunol***2016; 197(6):2219-28. doi: 10.4049/jimmunol.1600360.
29. Trenkmann M, Brock M, Gay RE, Michel BA, Gay S, Huber LC. Tumor necrosis factor α–induced microRNA-18a activates rheumatoid arthritis synovial fibroblasts through a feedback loop in NF-κB signaling. ***Arthritis Rheum***2013; 65(4):916-27. doi: 10.1002/art.37834.
30. Philippe L, Alsaleh G, Suffert G, Meyer A, Georgel P, Sibilia J. *et al*. TLR2 expression is regulated by microRNA miR-19 in rheumatoid fibroblast-like synoviocytes. ***J Immunology***2012; 188(1):454-61. doi: 10.4049/jimmunol.1102348.
31. Chen Y, Wang W, Chen Y, Tang Q, Zhu W, Li D. *et al*. MicroRNA-19a-3p promotes rheumatoid arthritis fibroblast-like synoviocytes via targeting SOCS3. ***J Cell Biochem***2019. doi: 10.1002/jcb.28442.
32. Philippe L, Alsaleh G, Pichot A, Ostermann E, Zuber G, Frisch B. *et al*. MiR-20a regulates ASK1 expression and TLR4-dependent cytokine release in rheumatoid fibroblast-like synoviocytes. ***Ann Rheum Dis***2013; 72(6):1071-79. doi: 10.1136/annrheumdis-2012-201654.
33. Terauchi R, Arai Y, Takahashi KA, Inoue A, Tonomura H, Asada H. *et al*. The effect of apoptosis signal-regulating kinase 1 gene transfer on rat collagen induced arthritis. ***J Rheumatol***2005; 32(12):2373-80.
34. Mnich SJ, Blanner PM, Hu LG, Shaffer AF, Happa FA, O'Neil S. *et al*. Critical role for apoptosis signal-regulating kinase 1 in the development of inflammatory K/BxN serum-induced arthritis. ***Int Immunopharmacol*** 2010; 10(10):1170-76. doi: 10.1016/j.intimp.2010.06.023.
35. Xie Z, Shen P, Qu Y, Xu J, Zheng C, Gao Y.*et al*. MiR-20a inhibits the progression of human arthritis fibroblast-like synoviocytes and inflammatory factor expression by targeting ADAM10. ***Environ Toxicol***2020; 35(8):867-78. doi: 10.1002/tox.22923.
36. Dong L, Wang X, Tan J, Li H, Qian W, Chen J. *et al*. Decreased expression of micro RNA-21 correlates with the imbalance of Th17 and Treg cells in patients with rheumatoid arthritis. ***J Cell Mol Med***2014; 18(11):2213-24. doi: 10.1111/jcmm.12353.
37. Chen Y, Xian PF, Yang L, Wang SX. MicroRNA-21 Promotes Proliferation of Fibroblast-Like Synoviocytes through Mediation of NF-κB Nuclear Translocation in a Rat Model of Collagen-Induced Rheumatoid Arthritis. ***Biomed Res Int***2016; 2016:9279078. doi: 10.1155/2016/9279078.
38. Lin J, Huo R, Xiao L, Zhu X, Xie J, Sun S. *et al*. A novel p53/microRNA-22/Cyr61 axis in synovial cells regulates inflammation in rheumatoid arthritis. ***Arthritis rheumatol***2014; 66(1):49-59. doi: 10.1002/art.38142.
39. 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. doi: 10.1016/j.gene.2019.144144.
40. Yang QY, Yang KP, Li ZZ. MiR-22 restrains proliferation of rheumatoid arthritis by targeting IL6R and may be concerned with the suppression of NF-κB pathway. ***Kaohsiung J Med Sci***2020; 36(1):20-26. doi: 10.1002/kjm2.12124.
41. Zhu S, Pan W, Song X, Liu Y, Shao X, Tang Y. *et al*. The microRNA miR-23b suppresses IL-17-associated autoimmune inflammation by targeting TAB2, TAB3 and IKK-α. ***Nat Med***2012; 18(7):1077-86. doi: 10.1038/nm.2815.
42. Xu K, Xu P, Yao J-F, Zhang Y-G, Hou W-k, Lu S-M. Reduced apoptosis correlates with enhanced autophagy in synovial tissues of rheumatoid arthritis. ***Inflamm Res***2013; 62(2):229-37. doi: 10.1007/s00011-012-0572-1.
43. Murata K, Furu M, Yoshitomi H, Ishikawa M, Shibuya H, Hashimoto M. *et al*. Comprehensive microRNA analysis identifies miR-24 and miR-125a-5p as plasma biomarkers for rheumatoid arthritis. ***PloS one***2013; 8(7):e69118. doi: 10.1371/journal.pone.0069118.
44. Niimoto T, Nakasa T, Ishikawa M, Okuhara A, Izumi B, Deie M. *et al*. MicroRNA-146a expresses in interleukin-17 producing T cells in rheumatoid arthritis patients. ***BMC musculoskelet Disord***2010; 11:209. doi: 10.1186/1471-2474-11-209.
45. Huang Z, Xing S, Liu M, Deng W, Wang Y, Huang Z. *et al*. MiR-26a-5p enhances cells proliferation, invasion, and apoptosis resistance of fibroblast-like synoviocytes in rheumatoid arthritis by regulating PTEN/PI3K/AKT pathway. ***Biosci Rep***2019; 39(7):BSR20182192. doi: 10.1042/BSR20182192.
46. Shi DL, Shi GR, Xie J, Du XZ, Yang H. MicroRNA-27a Inhibits Cell Migration and Invasion of Fibroblast-Like

Synoviocytes by Targeting Follistatin-Like Protein 1 in Rheumatoid Arthritis. ***Mol Cells***2016; 39(8):611-18. doi: 10.14348/molcells.2016.0103.

47.Liu J, Fei D, Xing J, Du J. MicroRNA-29a inhibits proliferation and induces apoptosis in rheumatoid arthritis fibroblast-like synoviocytes by repressing STAT3. ***Biomed Pharmacother***2017; 96:173-81. doi: 10.1016/j.biopha.2017.09.120.

48.Alsaleh G, François A, Philippe L, Gong YZ, Bahram S, Cetin S. *et al*. MiR-30a-3p negatively regulates BAFF synthesis in systemic sclerosis and rheumatoid arthritis fibroblasts. ***PLoS One***2014; 9(10):e111266. doi: 10.1371/journal.pone.0111266.

49.Niederer F, Trenkmann M, Ospelt C, Karouzakis E, Neidhart M, Stanczyk J. *et al*. Down-regulation of microRNA-34a* in rheumatoid arthritis synovial fibroblasts promotes apoptosis resistance. ***Arthritis Rheum***2012; 64(6):1771-79. doi: 10.1002/art.34334.

50.Wu H, Zhou X, Wang X, Cheng W, Hu X, Wang Y. *et al*. miR-34a in extracellular vesicles from bone marrow mesenchymal stem cells reduces rheumatoid arthritis inflammation via the cyclin I/ATM/ATR/p53 axis. ***J Cell Mol Med***2021; 25(4):1896-910. doi: 10.1111/jcmm.15857.

51.Song AF, Kang L, Wang YF, Wang M. MiR-34a-5p inhibits fibroblast‐like synoviocytes proliferation via XBP1. ***Eur Rev Med Pharmacol Sci***2020; 24(22):11675-82. doi: 10.26355/eurrev_202011_23812.

52.Hou C, Wang D, Zhang L. MicroRNA‐34a‐3p inhibits proliferation of rheumatoid arthritis fibroblast‐like synoviocytes. ***Mol Med Rep***2019; 20(3):2563-70. doi: 10.3892/mmr.2019.10516.

53.Wakisaka S, Suzuki N, Takeno M, Takeba Y, Nagafuchi H, Saito N. *et al*. Involvement of simultaneous multiple transcription factor expression, including cAMP responsive element binding protein and OCT-1, for synovial cell outgrowth in patients with rheumatoid arthritis. ***Ann Rheum Dis***1998; 57(8):487-94. doi: 10.1136/ard.57.8.487.

54.Lu MC, Yu CL, Chen HC, Yu HC, Huang HB, Lai NS. Increased miR-223 expression in T cells from patients with rheumatoid arthritis leads to decreased insulin-like growth factor-1-mediated interleukin-10 production. ***Clin Exp Immunol***2014; 177(3):641-51. doi: 10.1111/cei.12374.

55.Yu D, Tan AH-M, Hu X, Athanasopoulos V, Simpson N, Silva DG. *et al*. Roquin represses autoimmunity by limiting inducible T-cell co-stimulator messenger RNA. ***Nature***2007; 450(7167):299-03. doi: 10.1038/nature06253.

56.Wei Q, Lv F, Zhang H, Wang X, Geng Q, Zhang X. *et al*. MicroRNA-101-3p inhibits fibroblast-like synoviocyte proliferation and inflammation in rheumatoid arthritis by targeting PTGS2. ***Biosci Rep***2020; 40(1):BSR20191136. doi: 10.1042/BSR20191136.

57.Retraction: MicroRNA-101-3p inhibits fibroblast-like synoviocyte proliferation and inflammation in rheumatoid arthritis by targeting PTGS2. ***Biosci Rep***2020; 40(8):BSR-20191136_RET. doi: 10.1042/BSR-20191136_RET.

58.Anaparti V, Smolik I, Meng X, Spicer V, Mookherjee N, El-Gabalawy H. Whole blood microRNA expression pattern differentiates patients with rheumatoid arthritis, their seropositive first-degree relatives, and healthy unrelated control subjects. ***Arthritis Res Ther***2017; 19(1):249. doi: 10.1186/s13075-017-1459-x.

59.Nakamachi Y, Kawano S, Takenokuchi M, Nishimura K, Sakai Y, Chin T. *et al*. MicroRNA-124a is a key regulator of proliferation and monocyte chemoattractant protein 1 secretion in fibroblast-like synoviocytes from patients with rheumatoid arthritis. ***Arthritis Rheum***2009; 60(5):1294-04. doi: 10.1002/art.24475.

60.Yang B, Ge Y, Zhou Y, Wang J, Xie X, Li S. *et al*. miR-124a inhibits the proliferation and inflammation in rheumatoid arthritis fibroblast-like synoviocytes via targeting PIK3/NF-κB pathway. ***Cell Biochem Funct***2019; 37(4):208-15. doi: 10.1002/cbf.3386.

61.Kim S-W, Ramasamy K, Bouamar H, Lin A-P, Jiang D, Aguiar RC. MicroRNAs miR-125a and miR-125b constitutively activate the NF-κB pathway by targeting the tumor necrosis factor alpha-induced protein 3 (TNFAIP3, A20). ***Proc Natl AcadSci U S A***2012; 109(20):7865-70. doi: 10.1073/pnas.1200081109.

62.Wang H, Peng W, Ouyang X, Li W, Dai Y. Circulating microRNAs as candidate biomarkers in patients with systemic lupus erythematosus. ***Transl Res***2012; 160(3):198-06. doi: 10.1016/j.trsl.2012.04.002.

63.Gao J, Kong R, Zhou X, Ji L, Zhang J, Zhao D. MiRNA-126 expression inhibits IL-23R mediated TNF-α or IFN-γ production in fibroblast-like synoviocytes in a mice model of collagen-induced rheumatoid arthritis. ***Apoptosis***2018; 23(11-12):607-15. doi: 10.1007/s10495-018-1474-7.

64.Qu Y, Wu J, Deng JX, Zhang YP, Liang WY, Jiang ZL. *et al*. MicroRNA-126 affects rheumatoid arthritis synovial fibroblast proliferation and apoptosis by targeting PIK3R2 and regulating PI3K-AKT signal pathway. ***Oncotarget***2016; 7(45):74217-26. doi: 10.18632/oncotarget.12487.

65.Gao J, Zhou XL, Kong RN, Ji LM, He LL, Zhao DB. microRNA-126 targeting PIK3R2 promotes rheumatoid arthritis synovial fibro-blasts proliferation and resistance to apoptosis by regulating PI3K/AKT pathway. ***Exp Mol Pathol***2016; 100(1):192-98. doi: 10.1016/j.yexmp.2015.12.015.

66.Peng T, Ji D, Jiang Y. Long non-coding RNA GAS5 suppresses rheumatoid arthritis progression via miR-128-3p/HDAC4 axis. ***Mol Cell Biochem***2021;476(6):2491-501. doi: 10.1007/s11010-021-04098-1.

67.Du J, Zhang F, Guo J. miR‐137 decreases proliferation, migration and invasion in rheumatoid arthritis fibroblast‐like synoviocytes. ***Mol Med Rep***2018; 17(2):3312-17. doi: 10.3892/mmr.2017.8225.

68.Peng JS, Chen SY, Wu CL, Chong HE, Ding YC, Shiau AL. *et al*. Amelioration of Experimental Autoimmune Arthritis Through Targeting of Synovial Fibroblasts by Intraarticular Delivery of MicroRNAs 140-3p and 140-5p. ***Arthritis Rheumatol***2016; 68(2):370-81. doi: 10.1002/art.39446.

69.Zhu J, Wang J, Huang J, Du W, He Y, Pan H. *et al*. MicroRNA-140-5p regulates the proliferation, apoptosis and inflammation of RA FLSs by repressing STAT3. ***Exp Ther Med***2021; 21(2):171. doi: 10.3892/etm.2020.9602.

70.Dong S, Yang B, Guo H, Kang F. MicroRNAs regulate osteogenesis and chondrogenesis. ***Biochem Biophys Res Commun***2012; 418(4):587-91. doi: 10.1016/j.bbrc.2012.01.075.

71.Cheng Z, Liu F, Wang G, Li Y, Zhang H, Li F. miR-133 is a key negative regulator of CDC42–PAK pathway in gastric cancer. ***Cell Signal***2014; 26(12):2667-73. doi: 10.1016/j.cellsig.2014.08.012.

72.Qiang J, Lv T, Wu Z, Yang X. Down-regulation of microRNA-142-3p inhibits the aggressive phenotypes of

rheumatoid arthritis fibroblast-like synoviocytes through inhibiting nuclear factor-κB signaling. ***Biosci Rep***2019; 39(7):BSR20190700. doi: 10.1042/BSR20190700.

73. Hong BK, You S, Yoo SA, Park D, Hwang D, Cho CS. *et al*. MicroRNA-143 and -145 modulate the phenotype of synovial fibroblasts in rheumatoid arthritis. ***Exp Mol Med***2017; 49(8):e363. doi: 10.1038/emm.2017.108.
74. Yang Z, Wang J, Pan Z, Zhang Y. miR-143-3p regulates cell proliferation and apoptosis by targeting IGF1R and IGFBP5 and regulating the Ras/p38 MAPK signaling pathway in rheumatoid arthritis. ***Exp Ther Med***2018; 15(4):3781-90. doi: 10.3892/etm.2018.5907.
75. Su Y, Liu Y, Ma C, Guan C, Ma X, Meng S. Mesenchymal stem cell-originated exosomal lncRNA HAND2-AS1 impairs rheumatoid arthritis fibroblast-like synoviocyte activation through miR-143-3p/TNFAIP3/NF-κB pathway. ***J Orthop Surg Res***2021; 16(1):116. doi: 10.1186/s13018-021-02248-1.
76. Wang X, Tang K, Wang Y, Chen Y, Yang M, Gu C. *et al*. Elevated microRNA‑145‑5p increases matrix metalloproteinase‑9 by activating the nuclear factor‑κB pathway in rheumatoid arthritis. ***Mol Med Rep***2019; 20(3):2703-11. doi: 10.3892/mmr.2019.10499.
77. Li J, Wan Y, Guo Q, Zou L, Zhang J, Fang Y. *et al*. Altered microRNA expression profile with miR-146a upregulation in CD4+ T cells from patients with rheumatoid arthritis. ***Arthritis Res Ther***2010; 12(3):R81. doi: 10.1186/ar3006.
78. Nakasa T, Miyaki S, Okubo A, Hashimoto M, Nishida K, Ochi M. *et al*. Expression of microRNA-146 in rheumatoid arthritis synovial tissue. ***Arthritis Rheum***2008; 58(5):1284-92. doi: 10.1002/art.23429.
79. Abou-Zeid A, Saad M, Soliman E. MicroRNA 146a expression in rheumatoid arthritis: association with tumor necrosis factor–alpha and disease activity. ***GenetTestMol Biomarkers***2011; 15(11):807-12. doi: 10.1089/gtmb.2011.0026.
80. Filková M, Aradi B, Šenolt L, Ospelt C, Vettori S, Mann H. *et al*. Association of circulating miR-223 and miR-16 with disease activity in patients with early rheumatoid arthritis. ***Ann Rheum Dis***2014; 73(10):1898-904. doi: 10.1136/annrheumdis-2012-202815.
81. 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. ***Ann Rheum Dis***2015; 74(6):1265-74. doi: 10.1136/annrheumdis-2013-204377.
82. Lu L-F, Boldin MP, Chaudhry A, Lin L-L, Taganov KD, Hanada T. *et al*. Function of miR-146a in controlling Treg cell-mediated regulation of Th1 responses. ***Cell***2010; 142(6):914-29. doi: 10.1016/j.cell.2010.08.012.
83. Taganov KD, Boldin MP, Chang K-J, Baltimore D. NF-κB-dependent induction of microRNA miR-146, an inhibitor targeted to signaling proteins of innate immune responses. ***Proc Natl Acad Sci U S A***2006; 103(33):12481-86. doi: 10.1073/pnas.0605298103.
84. Hou J, Wang P, Lin L, Liu X, Ma F, An H. *et al*. MicroRNA-146a feedback inhibits RIG-I-dependent Type I IFN production in macrophages by targeting TRAF6, IRAK1, and IRAK2. ***JImmunol*** 2009; 183(3):2150-58. doi: 10.4049/jimmunol.0900707.
85. Curtale G, Citarella F, Carissimi C, Goldoni M, Carucci N, Fulci V. *et al*. An emerging player in the adaptive immune response: microRNA-146a is a modulator of IL-2 expression and activation-induced cell death in T lymphocytes. ***Blood*** 2010; 115(2):265-73. doi: 10.1182/ lymphocytes. ***Blood*** 2010; 115(2):265-73. doi: 10.1182/ blood-2009-06-225987.
86. Zhang Z, Jimi E, Bothwell AL. Receptor activator of NF-κB ligand stimulates recruitment of SHP-1 to the complex containing TNFR-associated factor 6 that regulates osteoclastogenesis. ***J Immunol*** 2003; 171(7): 3620-26. doi: 10.4049/jimmunol.171.7.3620.
87. Yen M-L, Hsu P-N, Liao H-J, Lee B-H, Tsai H-F. TRAF-6 dependent signaling pathway is essential for TNF-related apoptosis-inducing ligand (TRAIL) induces osteoclast differentiation. ***PLoS One*** 2012; 7(6):e38048. doi: 10.1371/journal.pone.0038048.
88. Nakasa T, Shibuya H, Nagata Y, Niimoto T, Ochi M. The inhibitory effect of microRNA-146a expression on bone destruction in collagen-induced arthritis. ***Arthritis Rheum*** 2011; 63(6):1582-90. doi: 10.1002/art.30321.
89. Wang W, Shao S, Jiao Z, Guo M, Xu H, Wang S. The Th17/Treg imbalance and cytokine environment in peripheral blood of patients with rheumatoid arthritis. ***Rheumatol Int*** 2012; 32(4):887-93. doi: 10.1007/s00296-010-1710-0.
90. Niu Q, Cai B, Huang Z-c, Shi Y-y, Wang L-l. Disturbed Th17/Treg balance in patients with rheumatoid arthritis. ***Rheumatol Int*** 2012; 32(9):2731-36. doi: 10.1007/ s00296-011-1984-x.
91. Qiu M, Mo L, Li J, Liang H, Zhu W, Zheng X. *et al*. Effects of miR-150-5p on the growth and SOCS1 expression of rheumatoid arthritis synovial fibroblasts. ***Clin Rheumatol*** 2020; 39(3):909-17. doi: 10.1007/ s10067-019-04894-7.
92. Guo J, Du J, Fei D, Xing J, Liu J, Lu H. miR‑152 inhibits rheumatoid arthritis synovial fibroblast proliferation and induces apoptosis by targeting ADAM10. ***Int J Mol Med*** 2018; 42(1):643-50. doi: 10.3892/ijmm.2018.3636.
93. Miao CG, Qin D, Du CL, Ye H, Shi WJ, Xiong YY. *et al*. DNMT1 activates the canonical Wnt signaling in rheumatoid arthritis model rats via a crucial functional crosstalk between miR-152 and the DNMT1, MeCP2. ***Int Immunopharmacol*** 2015; 28(1):344-53. doi: 10.1016/ j.intimp.2015.06.013.
94. Miao CG, Yang YY, He X, Huang C, Huang Y, Qin D. *et al*. MicroRNA-152 modulates the canonical Wnt pathway activation by targeting DNA methyltransferase 1 in arthritic rat model. ***Biochimie*** 2014; 106:149-56. doi: 10.1016/j.biochi.2014.08.016.
95. Kurowska-Stolarska M, Alivernini S, Ballantine LE, Asquith DL, Millar NL, Gilchrist DS. *et al*. MicroRNA-155 as a proinflammatory regulator in clinical and experimental arthritis. ***Proc Natl Acad Sci U S A***2011; 108(27):11193-98. doi: 10.1073/pnas.1019536108.
96. Pandis I, Ospelt C, Karagianni N, Denis MC, Reczko M, Camps C. *et al*. Identification of microRNA-221/222 and microRNA-323-3p association with rheumatoid arthritis via predictions using the human tumour necrosis factor transgenic mouse model. ***Ann Rheum Dis*** 2012; 71(10):1716-23. doi: 10.1136/ annrheumdis-2011-200803.
97. McCoy CE, Sheedy FJ, Qualls JE, Doyle SL, Quinn SR, Murray PJ. *et al*. IL-10 inhibits miR-155 induction by toll-like receptors. ***J Biol Chem***2010; 285(27):20492-98. doi: 10.1074/jbc.M110.102111.
98. Li X, Tian F, Wang F. Rheumatoid arthritis-associated microRNA-155 targets SOCS1 and upregulates TNF-α and IL-1β in PBMCs. ***Int JMol Sci***2013; 14(12):23910-21. doi: 10.3390/ijms141223910.
99. Smigielska-Czepiel K, van den Berg A, Jellema P, van der Lei RJ, Bijzet J, Kluiver J. *et al*. Comprehensive

analysis of miRNA expression in T-cell subsets of rheumatoid arthritis patients reveals defined signatures of naive and memory Tregs. ***Genes Immun*** 2014; 15(2):115-25. doi: 10.1038/gene.2013.69

100.Yao R, Ma Y-L, Liang W, Li H-H, Ma Z-J, Yu X. *et al*. MicroRNA-155 modulates Treg and Th17 cells differentiation and Th17 cell function by targeting SOCS1. ***PloS one*** 2012; 7(10):e46082. doi: 10.1371/ journal.pone.0046082.

101.Vigorito E, Perks KL, Abreu-Goodger C, Bunting S, Xiang Z, Kohlhaas S. *et al*. microRNA-155 regulates the generation of immunoglobulin class-switched plasma cells. ***Immunity*** 2007; 27(6):847-59.doi: 10.1016/ j.immuni.2007.10.009.

102.Migita K, Iwanaga N, Izumi Y, Kawahara C, Kumagai K, Nakamura T. *et al*. TNF-α-induced miR-155 regulates IL-6 signaling in rheumatoid synovial fibroblasts. ***BMC Res Notes*** 2017; 10(1):403. doi: 10.1186/s13104-017-2715-5.

103.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. ***Exp Ther Med*** 2020; 19(2):1288-96. doi: 10.3892/etm.2019.8330.

104.Sonkoly E, Janson P, Majuri M-L, Savinko T, Fyhrquist N, Eidsmo L. *et al*. MiR-155 is overexpressed in patients with atopic dermatitis and modulates T-cell proliferative responses by targeting cytotoxic T lymphocyte–associated antigen 4. ***J Allergy Clin Immunol*** 2010; 126(3):581-89. e1-20. doi: 10.1016/ j.jaci.2010.05.045.

105.O'Connell RM, Kahn D, Gibson WS, Round JL, Scholz RL, Chaudhuri AA. *et al*. MicroRNA-155 promotes autoimmune inflammation by enhancing inflammatory T cell development. ***Immunity*** 2010; 33(4):607-19. doi: 10.1016/j.immuni.2010.09.009.

106.Wu T, Xie M, Wang X, Jiang X, Li J, Huang H. miR-155 modulates TNF-α-inhibited osteogenic differentiation by targeting SOCS1 expression. ***Bone***2012; 51(3):498-05. doi: 10.1016/j.bone.2012.05.013.

107.Mizoguchi F, Izu Y, Hayata T, Hemmi H, Nakashima K, Nakamura T. *et al*. Osteoclast-specific Dicer gene deficiency suppresses osteoclastic bone resorption. ***J Cell Biochem*** 2010; 109(5):866-75. doi: 10.1002/jcb.22228.

108.Blüml S, Bonelli M, Niederreiter B, Puchner A, Mayr G, Hayer S. *et al*. Essential role of microRNA-155 in the pathogenesis of autoimmune arthritis in mice. ***Arthritis Rheum*** 2011; 63(5):1281-88.doi: 10.1002/art.30281.

109.Lu L-F, Thai T-H, Calado DP, Chaudhry A, Kubo M, Tanaka K. *et al*. Foxp3-dependent microRNA155 confers competitive fitness to regulatory T cells by targeting SOCS1 protein. ***Immunity*** 2009; 30(1):80-91. doi: 10.1016/j.immuni.2008.11.010.

110.Michou L, Lasbleiz S, Rat A-C, Migliorini P, Balsa A, Westhovens R. *et al*. Linkage proof for PTPN22, a rheumatoid arthritis susceptibility gene and a human autoimmunity gene. ***Proc Natl Acad Sci U S A***2007; 104(5):1649-54. doi: 10.1073/pnas.0610250104.

111.Li G, Yu M, Lee W-W, Tsang M, Krishnan E, Weyand CM. *et al*. Decline in miR-181a expression with age impairs T cell receptor sensitivity by increasing DUSP6 activity. ***Nat Med*** 2012; 18(10):1518-24. doi: 10.1038/ nm.2963.

112.Gregersen PK, Batliwalla F: PTPN22 and rheumatoid arthritis: gratifying replication. In.: Wiley Online Library; 2005.

113.Ruedel A, Dietrich P, Schubert T, Hofmeister S, Hellerbrand C, Bosserhoff AK. Expression and function

113.Ruedel A, Dietrich P, Schubert T, Hofmeister S, Hellerbrand C, Bosserhoff AK. Expression and function of microRNA-188-5p in activated rheumatoid arthritis synovial fibroblasts. ***Int J Clin Exp Pathol***2015; 8(5):4953-62.

114.Li S, Jin Z, Lu X. MicroRNA-192 suppresses cell proliferation and induces apoptosis in human rheumatoid arthritis fibroblast-like synoviocytes by downregulating caveolin 1. ***Mol Cell Biochem*** 2017; 432(1-2):123-30. doi: 10.1007/s11010-017-3003-3.

115.Wangyang Y, Yi L, Wang T, Feng Y, Liu G, Li D. *et al*. MiR-199a-3p inhibits proliferation and induces apoptosis in rheumatoid arthritis fibroblast-like synoviocytes via suppressing retinoblastoma 1. ***Biosci Rep*** 2018; 38(6):BSR20180982. doi: 10.1042/ BSR20180982.

116.Stanczyk J, Ospelt C, Karouzakis E, Filer A, Raza K, Kolling C. *et al*. Altered expression of microRNA-203 in rheumatoid arthritis synovial fibroblasts and its role in fibroblast activation. ***Arthritis Rheum*** 2011; 63(2):373-81. doi: 10.1002/art.30115.

117.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. ***J Biol Res (Thessalon)*** 2021; 28(1):1. doi: 10.1186/s40709-020-00131-4.

118.Li B, Li N, Zhang L, Li K, Xie Y, Xue M. *et al*. Hsa_circ_0001859 Regulates ATF2 Expression by Functioning as an MiR-204/211 Sponge in Human Rheumatoid Arthritis. ***J Immunol Res*** 2018; 2018:9412387. doi: 10.1155/2018/9412387.

119.Xiao J, Wang R, Zhou W, Cai X, Ye Z. LncRNA NEAT1 regulates the proliferation and production of the inflammatory cytokines in rheumatoid arthritis fibroblast-like synoviocytes by targeting miR-204-5p. ***Hum Cell*** 2021; 34(2):372-82. doi: 10.1007/s13577-020- 00461-4.

120.Liu Y, Zhang XL, Li XF, Tang YC, Zhao X. miR-212-3p reduced proliferation, and promoted apoptosis of fibroblast-like synoviocytes via down-regulating SOX5 in rheumatoid arthritis. ***Eur Rev Med Pharmacol Sci*** 2018; 22(2):461-71. doi: 10.26355/eurrev_ 201801_ 14196.

121.Iwamoto N, Fukui S, Takatani A, Shimizu T, Umeda M, Nishino A. *et al*. Osteogenic differentiation of fibroblast-like synovial cells in rheumatoid arthritis is induced by microRNA-218 through a ROBO/Slit pathway. ***Arthritis Res Ther*** 2018; 20(1):189. doi: 10.1186/s13075-018-1703-z.

122.Yang S, Yang Y. Downregulation of microRNA‐221 decreases migration and invasion in fibroblast‐like synoviocytes in rheumatoid arthritis. ***Mol Med Rep*** 2015; 12(2):2395-01. doi: 10.3892/mmr.2015.3642.

123.Maeda Y, Farina NH, Matzelle MM, Fanning PJ, Lian JB, Gravallese EM. Synovium-derived microRNAs regulate bone pathways in rheumatoid arthritis. ***J Bone Miner Res*** 2017; 32(3):461-72. doi: 10.1002/jbmr.3005.

124.Shibuya H, Nakasa T, Adachi N, Nagata Y, Ishikawa M, Deie M. *et al*. Overexpression of microRNA-223 in rheumatoid arthritis synovium controls osteoclast differentiation. ***Mod Rheumatol*** 2013; 23(4):674-85. doi: 10.1007/s10165-012-0710-1.

125.Sugatani T, Hruska KA. Impaired micro-RNA pathways diminish osteoclast differentiation and function. ***J Biol Chem*** 2009; 284(7):4667-78. doi: 10.1074/jbc.M805777200.

126.Fulci V, Scappucci G, Sebastiani GD, Giannitti C, Franceschini D, Meloni F. *et al*. miR-223 is overexpressed in T-lymphocytes of patients affected by rheumatoid arthritis. ***Hum Immunol*** 2010; 71(2):206-11.

doi: 10.1016/j.humimm.2009.11.008.

127.Sebastiani GD, Fulci V, Niccolini S, Giannitti C, Bugatti S, Minisola G. *et al*. Over-expression of miR-223 in T-lymphocytes of early rheumatoid arthritis patients. ***Clin Exp Rheumatol*** 2011; 29(6):1058-59.

128.Li YT, Chen SY, Wang CR, Liu MF, Lin CC, Jou IM. *et al*. Brief Report: Amelioration of collagen-induced arthritis in mice by lentivirus-mediated silencing of microRNA-223. ***Arthritis Rheum*** 2012; 64(10):3240-45. doi: 10.1002/art.34550.

129.Moriya N, Shibasaki S, Karasaki M, Iwasaki T. The Impact of MicroRNA-223-3p on IL-17 Receptor D Expression in Synovial Cells. ***PLoS One*** 2017; 12(1):e0169702. doi: 10.1371/journal.pone.0169702.

130.Wu ZM, Luo J, Shi XD, Zhang SX, Zhu XB, Guo J. Icariin alleviates rheumatoid arthritis via regulating miR-223-3p/NLRP3 signalling axis. ***Autoimmunity*** 2020; 53(8):450-58. doi: 10.1080/08916934.2020.1836488.

131.Tang X, Yin K, Zhu H, Tian J, Shen D, Yi L. *et al*. Correlation Between the Expression of MicroRNA-301a-3p and the Proportion of Th17 Cells in Patients with Rheumatoid Arthritis. ***Inflammation*** 2016; 39(2):759-67. doi: 10.1007/s10753-016-0304-8.

132.Lin K, Su HY, Jiang LF, Chu TG, Li Z, Chen XL. *et al*. Influences of miR-320a on proliferation and apoptosis of fibroblast-like synoviocytes in rheumatoid arthritis through targeting MAPK-ERK1/2. ***Eur Rev Med Pharmacol Sci*** 2019; 23(5):1907-14. doi: 10.26355/ eurrev_201903_17228.

133.Xu T, Li L, Huang C, Li X, Peng Y, Li J. MicroRNA-323-3p with clinical potential in rheumatoid arthritis, Alzheimer's disease and ectopic pregnancy. ***Expert Opin Ther Targets*** 2014; 18(2):153-58. doi: 10.1517/14728222.2014.855201.

134.Guo T, Ding H, Jiang H, Bao N, Zhou L, Zhao J. miR-338-5p Regulates the Viability, Proliferation, Apoptosis and Migration of Rheumatoid Arthritis Fibroblast-Like Synoviocytes by Targeting NFAT5. ***Cell Physiol Biochem*** 2018; 49(3):899-10. doi: 10.1159/000493222.

135.Zhang S, Meng T, Tang C, Li S, Cai X, Wang D. *et al*. MicroRNA-340-5p suppressed rheumatoid arthritis synovial fibroblast proliferation and induces apoptotic cell number by targeting signal transducers and activators of transcription 3. ***Autoimmunity*** 2020; 53(6):314-22. doi: 10.1080/08916934.2020.1793134.

136.Alsaleh G, Suffert G, Semaan N, Juncker T, Frenzel L, Gottenberg J-E. *et al.* Bruton's tyrosine kinase is involved in miR-346-related regulation of IL-18 release by lipopolysaccharide-activated rheumatoid fibroblast-like synoviocytes. ***J Immunol*** 2009; 182(8):5088-97. doi: 10.4049/jimmunol.0801613.

137.Semaan N, Frenzel L, Alsaleh G, Suffert G, Gottenberg JE, Sibilia J. *et al*. miR-346 controls release of TNF-α protein and stability of its mRNA in rheumatoid arthritis via tristetraprolin stabilization. ***PLoS One*** 2011; 6(5):e19827. doi: 10.1371/journal.pone.0019827.

138.Miao CG, Shi WJ, Xiong YY, Yu H, Zhang XL, Qin MS. *et al*. miR-375 regulates the canonical Wnt pathway through FZD8 silencing in arthritis synovial fibroblasts. ***Immunol Lett*** 2015; 164(1):1-10. doi: 10.1016/ j.imlet.2015.01.003.

139.Zhi L, Liang J, Huang W, Ma J, Qing Z, Wang X. Circ_AFF2 facilitates proliferation and inflammatory response of fibroblast-like synoviocytes in rheumatoid arthritis via the miR-375/TAB2 axis. ***Exp Mol Pathol 2021;*** 119:104617. doi: 10.1016/j. yexmp. 2021. 104617.

140.Wang Y, Xu N, Zhao S, Jiao T, Fu W, Yang L. et al. miR-410-3p Suppresses Cytokine Release from Fibroblast-Like Synoviocytes by Regulating NF-κB Signaling in Rheumatoid Arthritis. ***Inflammation*** 2019; 42(1):331-41. doi: 10.1007/s10753-018-0896-2.

141.Wang Y, Jiao T, Fu W, Zhao S, Yang L, Xu N. *et al*. miR-410-3p regulates proliferation and apoptosis of fibroblast-like synoviocytes by targeting YY1 in rheumatoid arthritis. ***Biomed Pharmacother*** 2019; 119:109426. doi: 10.1016/j.biopha.2019.109426.

142.Murata K, Yoshitomi H, Furu M, Ishikawa M, Shibuya H, Ito H. *et al*. MicroRNA-451 down-regulates neutrophil chemotaxis via p38 MAPK. ***Arthritis rheumatol*** 2014; 66(3):549-59. doi: 10.1002/art.38269.

143.Wang Y, Hou L, Yuan X, Xu N, Zhao S, Yang L. *et al*. miR-483-3p promotes cell proliferation and suppresses apoptosis in rheumatoid arthritis fibroblast-like synoviocytes by targeting IGF-1. ***Biomed Pharmacother*** 2020; 130:110519. doi: 10.1016/j.biopha.2020.110519.

144.Fang L, Xu XF, Lu Y, Wu YY, Li JJ. MicroRNA-495 attenuates proliferation and inflammatory response in rheumatoid arthritis fibroblast-like synoviocytes through attenuating β-catenin pathway. ***J Biol Regul Homeost Agents*** 2020; 34(3):837-44. doi: 10.23812/20-47-a-22.

145.Li D, Zhou Q, Hu G, Wang G. MiRNA-506 inhibits rheumatoid arthritis fibroblast-like synoviocytes proliferation and induces apoptosis by targetting TLR4. ***Biosci Rep*** 2019; 39(5):BSR20182500. doi: 10.1042/ BSR20182500.

146.Wang X, Si X, Sun J, Yue L, Wang J, Yu Z. miR-522 Modulated the Expression of Proinflammatory Cytokines and Matrix Metalloproteinases Partly via Targeting Suppressor of Cytokine Signaling 3 in Rheumatoid Arthritis Synovial Fibroblasts. ***DNA Cell Biol*** 2018; 37(4):405-15. doi: 10.1089/dna.2017.4008.

147.Liu Y, Qian K, Li C, Ma Y, Chen X. Roles of microRNA-539 and osteopontin in rheumatoid arthritis. ***Exp Ther Med*** 2018; 15(3):2681-87. doi: 10.3892/ etm.2017.5665.

148.Wang Y, Zheng F, Gao G, Yan S, Zhang L, Wang L. *et al*. MiR-548a-3p regulates inflammatory response via TLR4/NF-κB signaling pathway in rheumatoid arthritis. ***J Cell Biochem***2018. doi: 10.1002/jcb.26659.

149.Wang L, Song G, Zheng Y, Wang D, Dong H, Pan J. *et al*. miR-573 is a negative regulator in the pathogenesis of rheumatoid arthritis. ***Cell Mol Immunol*** 2016; 13(6):839-49. doi: 10.1038/cmi.2015.63.

150.Wang L, Song G, Tan W, Qi M, Zhang L, Chan J. *et al*. MiR-573 inhibits prostate cancer metastasis by regulating epithelial-mesenchymal transition. ***Oncotarget*** 2015; 6(34):35978-90. doi: 10.18632/oncotarget.5427.

151.Liu L, Zuo Y, Xu Y, Zhang Z, Li Y, Pang J. MiR-613 inhibits proliferation and invasion and induces apoptosis of rheumatoid arthritis synovial fibroblasts by direct down-regulation of DKK1. ***Cell Mol Biol Lett*** 2019; 24:8. doi: 10.1186/s11658-018-0130-0.

152.Xu X, Chen H, Zhang Q, Xu J, Shi Q, Wang M. MiR-650 inhibits proliferation, migration and invasion of rheumatoid arthritis synovial fibroblasts by targeting AKT2. ***Biomed Pharmacother*** 2017; 88:535-41. doi: 10.1016/j.biopha.2017.01.063.

153.Qu W, Jiang L, Hou G. Circ-AFF2/miR-650/CNP axis promotes proliferation, inflammatory response, migration, and invasion of rheumatoid arthritis synovial fibroblasts. ***J Orthop Surg Res***2021; 16(1):165. doi: 10.1186/s13018-021-02306-8.

154.Miao CG, Shi WJ, Xiong YY, Yu H, Zhang XL, Qin

154.Miao CG, Shi WJ, Xiong YY, Yu H, Zhang XL, Qin MS. *et al*. MicroRNA-663 activates the canonical Wnt signaling through the adenomatous polyposis coli suppression. ***Immunol Lett*** 2015; 166(1):45-54. doi: 10.1016/j.imlet.2015.05.011.

155.Mookherjee N, El-Gabalawy HS. High degree of correlation between whole blood and PBMC expression levels of miR-155 and miR-146a in healthy controls and rheumatoid arthritis patients. ***J Immunol Methods*** 2013; 400-401:106-10. doi: 10.1016/j.jim.2013.10.001.

156.Duroux-Richard I, Pers Y-M, Fabre S, Ammari M, Baeten D, Cartron G. *et al*. Circulating miRNA-125b is a potential biomarker predicting response to rituximab in rheumatoid arthritis. ***Mediators Inflamm*** 2014; 2014:342524. doi: 10.1155/2014/342524.

157.Zhu S, Pan W, Song X, Liu Y, Shao X, Tang Y. *et al*. The microRNA miR-23b suppresses IL-17-associated autoimmune inflammation by targeting TAB2, TAB3 and IKK-α. ***Nat Med*** 2012; 18(7):1077-86. doi: 10.1038/ nm.2815.

158.Ouboussad L, Hunt L, Hensor E, Nam J, Barnes N, Emery P. *et al*. Profiling microRNAs in individuals at risk of progression to rheumatoid arthritis. ***Arthritis Res Ther*** 2017; 19(1):288. doi: 10.1186/s13075-017-1492-9.

159.Lenert A, Fardo DW. Detecting novel micro RNAs in rheumatoid arthritis with gene-based association testing. ***Clin Exp Rheumatol*** 2017; 35(4):586-92.

160.Bao X, Ma L, He C. MicroRNA-23a-5p regulates cell proliferation, migration and inflammation of TNF-α-stimulated human fibroblast-like MH7A synoviocytes by targeting TLR4 in rheumatoid arthritis. ***Exp Ther Med*** 2021; 21(5):479. doi: 10.3892/etm.2021.9910.

161.ElAtta ASA, Ali YB, Bassyouni IH, Talaat RM. Upregulation of miR-221/222 expression in rheumatoid arthritis (RA) patients: Correlation with disease activity. ***Clin Exp Med*** 2019; 19(1):47-53. doi: 10.1007/s10238-018-0524-3.

162.Chen Y, Wang X, Yang M, Ruan W, Wei W, Gu D. *et al*. miR-145-5p increases osteoclast numbers in vitro and aggravates bone erosion in collagen-induced arthritis by targeting osteoprotegerin. ***Med Sci Monit*** 2018; 24:5292-00. doi: 10.12659/MSM.908219.

163.Ebrahimiyan H, Rezaei N, Vojdanian M, Aslani S, Jamshidi A, Mahmoudi M. microRNA involvement in the regulation of survivin in peripheral blood mononuclear cells from rheumatoid arthritis patients. ***Int JRheum Dis*** 2019; 22(6):1107-14. doi: 10.1111/1756-185X.13520.

164.Al-Sadi AM, Al-Oweisi FA, Edwards SG, Al-Nadabi H, Al-Fahdi AM. Genetic analysis reveals diversity and genetic relationship among Trichoderma isolates from potting media, cultivated soil and uncultivated soil. ***BMC microbiol*** 2015; 15(1):147. doi: 10.1186/s12866-015-0483-8.

165.Vickers NJ. Animal communication: when i'm calling you, will you answer too? ***Curr Biol*** 2017; 27(14):R713-15. doi: 10.1016/j.cub.2017.05.064.

166.Jing W, Zhang X, Sun W, Hou X, Yao Z, Zhu Y. CRISPR/CAS9-mediated genome editing of miRNA-155 inhibits proinflammatory cytokine production by RAW264. 7 cells. ***Biomed Res Int*** 2015; 2015:326042. doi: 10.1155/2015/326042.