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Review

MicroRNAs in rheumatoid arthritis: From pathogenesis to clinical impact

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ABSTRACT

Over the last decade, many epigenetic mechanisms that contribute in the pathogenesis of autoimmune disorders have been revealed. MicroRNAs (miRNAs) are small, non-coding, RNA molecules that bind to messenger RNAs and disrupt the transcription of target genes. Rheumatoid arthritis (RA) is a chronic systemic autoimmune disease in which a plethora of epigenetic changes take place. Current research on RA epigenetics has focused mainly on miRNAs. Genetic variance of some miRNA genes, especially miR-499, might predispose an individual to RA development. Additionally, altered expression of many miRNAs has been discovered in several cells, tissues and body fluids in patients with RA. MiRNAs expression also differs depending on disease's stage and activity. Serum miR-22 and miR-103a might predict RA development in susceptible individuals (pre-RA), while serum miR-16, miR-24, miR-125a and miR-223 levels are altered in early RA (disease duration <12 months) patients compared to established RA or healthy individuals. Moreover, serum miR-223 levels have been associated with RA activity and disease relapse. What is more, serum levels of several miRNAs, including miR-125b and miR-223, could be used to predict response to RA treatment. Finally, miRNA analogs or antagonists have been used as therapeutic regimens in experimental arthritis models and have demonstrated promising results. In conclusion, the research on the miRNA alterations in RA sheds light to several aspects of RA pathogenesis, introduces new biomarkers for RA diagnosis and treatment response prediction and offers the opportunity to discover new, targeted drugs for patients with RA.

List of Abbreviations

CD4	Cluster of differentiation 4
DMARDs	Disease modifying anti-rheumatic drugs
DAS28	Disease Activity Score 28
JAK/STAT	Janus kinase/signal transducer and activator of transcription proteins
MMPs	Matrix metalloproteinases
NF-κB	Nuclear factor kappa beta
OA	Osteoarthritis
PBMCs	peripheral blood mononuclear cells
RA	Rheumatoid Arthritis
RASFs	rheumatoid arthritis synovial fibroblasts
SNPs	Single-nucleotide polymorphisms
Th17	T helper 17 cells
TLR	toll-like receptor
TNF	Tumor Necrosis Factor
Tregs	T regulatory cells
Wnt	Wingless/Integrated

1. Introduction

Rheumatoid arthritis (RA) is a chronic systematic autoimmune disorder that is characterized by joint inflammation leading, if left untreated, to musculoskeletal deformities, impaired functionality and high morbidity [1]. During the last decade, a growing body of evidence has shown that epigenetic mechanisms, the most widely investigated of which is the microRNAs, contribute significantly in RA pathogenesis [2–4].

MicroRNAs (miRNAs) are small non-coding RNA molecules that are implicated to post-transcriptional gene expression regulation. miRNAs bind to messenger RNAs (mRNAs) that have complementary sequences

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Table 1
Changes of miRNA levels in PBMCs. The changes of miRNA levels in PBMCs, as well as the suggested target mRNAs and the output observed are presented (**Legend**: NA: Not available data, **PBMCs**: Peripheral Blood Mononuclear Cells, **K-Ras**: Kirsten RAt Sarcoma virus gene, **ERK1/2**: Extracellular signal-regulated kinase 1/2, **JNK**: c-Jun N-terminal kinase, **STAT**: Signal transducer and activator of transcription, **Foxp3**: Forkhead box P3, **IL-1**: Interleukin-1, **Th17**: T helper 17 cells, **Treg**: T regulatory cells, **IRAK1**: Interleukin-1 receptor-associated kinase 1, **TRAF6**: tumor necrosis factor receptor-associated factor 6, **SHIP-1**: Src homology 2-containing inositol phosphatase-1, **SOCS1**: Suppressor of cytokine signaling 1, **CASP10**: Caspase 10, **APAF1**: Apoptotic protease activating factor 1, **PIAS3**: Protein inhibitor of activated STAT3, **TLR**: Toll-like Receptor, **NF-κB**: Nuclear factor kappa beta).

miRNA	Change	Target gene(s)	Results	Reference
let-7a	Decline	K-Ras, ERK1/2, JNK	↑IL-1	[36]
miR-16	Incline	NA	NA	[22]
miR-21	Decline	STAT3, STAT5, Foxp3	↑Th17, ↓Treg	[33]
miR-103a	Incline	TP53, AGO2	NA	[20]
miR-125b	Decline	NA	NA	[34]
miR-132	Incline	NA	NA	[22]
miR-145	Incline	NA	↑Bone erosions	[23]
miR-146a	Incline	IRAK1, TRAF6	↑Pro-inflammatory cytokines	[22,24]
miR-155	Incline	SHIP-1, SOCS1, CASP10, APAF1	↑TNFa, IL-1 ↓PBMCs apoptosis	[22,25–30]
miR-221	Incline	NA	NA	[31]
miR-222	Incline	NA	NA	[31]
miR-301a	Incline	PIAS3	↑Th17 differentiation, ↑proinflammatory cytokines	[32]
miR-548a	Decline	TLR-4/NF-κB	↑NF-κB mediated inflammation	[35]

and inhibit their translation, suppressing the production of specific proteins. Apart from regulating normal cellular processes, miRNAs seem to have a disturbed expression in several cells and body compartments in patients with autoimmune disorders [2–7]. Altered miRNA expression has been associated with enhanced inflammatory pathway signaling, increased secretion of pro-inflammatory cytokines and other processes that preserve the vicious cycle of autoimmunity [8].

Many researchers have investigated the role of several miRNAs in patients with RA or in animal models. The aim of this review is not only to focus on the role of miRNAs in RA pathogenesis, but also demonstrate the possible applications of miRNA for RA patients in clinical practice.

2. Methods

An online search in Medline database through PubMed was conducted by four independent investigators using the keywords “microRNA” and “rheumatoid arthritis”. Papers published from January 2008 to December 2018 were included. After screening titles and abstracts, full texts of the selected articles were scrutinized. References of included papers were also checked for related publications. Original articles or reviews written in other language than English were excluded.

3. The role of mirnas in RA pathogenesis

3.1. Genetic predisposition

The genetic background is known to play an important role in RA susceptibility [9]. Several studies have been conducted in different populations, mainly Chinese [10], Egyptian [11–13], Iranian [14], Polish [15] and Mexican [16] and examined the following SNPs: rs2910164 (G/C) of miR-146a gene, rs11614913 (C/T) of miR-196a2 gene and rs3746444 (T/C) of miR-499 gene. Meta-analyses dealt with the same issue [17]. What is more, the SNP rs3027898 (A/C) in the gene of IL-1 receptor-associated kinase 1 (IRAK-1), a protein-target of miR-146a, has been also examined in patients with RA [8]. Collectively, miR-499 gene and IRAK-1 gene alterations might be connected with increased risk for RA development, while the examined SNP in miR-146a does not seem to play a role in RA susceptibility.

3.2. Early stages of RA

A chronic subclinical period of systemic inflammation precedes the clinical presentation of RA. Anti-citrullinated protein antibodies (ACPAs) can be found in serum of RA patients even 5 years before arthritis development [18]. Patients with positive ACPAs that complain for non-specific musculoskeletal symptoms other than arthritis are in increased risk for RA development (pre-RA) [17]. Amongst the latter, the levels of miR-22, miR-38 and miR-486 in serum were elevated in those who finally developed RA and this was more pronounced for miR-22 [19]. In addition, patients with “seropositive” RA (positive ACPAs or rheumatoid factor - RF) and first-degree relatives with positive ACPAs share common serum miRNA “signature” that differentiates them from healthy individuals; especially miR-103a levels remained increased in both patients and seropositive relatives throughout a one-year follow-up period [20]. In conclusion, elevated serum levels of miR-22 and miR-103a might be used to predict RA development in individuals with positive ACPAs.

miRNA expression differs between patients with early RA (ERA, defined as disease with less of 12 months symptom duration) and patients with established disease. In ERA, serum levels of miR-16, miR-146a, miR-155 and miR-223 are lower than in established RA [21]. Moreover, patients with ERA have significantly lower serum levels of miR-16 and miR-223 compared to healthy controls, so these two miRNAs could serve as biomarkers to distinguish patients with ERA from healthy individuals [21].

3.3. Peripheral blood mononuclear cells

Many changes of miRNA levels in peripheral blood mononuclear cells (PBMCs) of RA patients have been reported (Table 1). miR-16 [22], miR-103a [20], miR-132 [22], miR-145 [23], miR-146a [22,24], miR-155 [22,25–30], miR-221 [31], miR-222 [31] and miR-301a [32] have been found elevated, while miR-21 [33], miR-125b [34] and miR-548a [35] are decreased in PBMCs of patients with RA. These alterations lead mainly in enhanced cytokine secretion and in disturbed Th17-Tregs balance in peripheral blood. Interestingly, miR-146a overexpression does not influence the levels of IRAK-1 and tumor necrosis factor receptor-associated factor (TRAF) in PBMCs [22], which participate in down-regulation of IL-1 and TNFa production, respectively. Thus, this dysregulation in PBMCs might contribute in the persistent proinflammatory cytokine production in RA patients [24]. Additionally, ACPA provoke an increase in IL-1β production from peripheral monocytes through a decline in let-7a in these cells [36]. It appears that let-

7a is much less expressed in peripheral monocytes of ACPA-positive patients compared to ACPA-negative patients [36].

Extracellular Vesicles (EVs) derived from PBMCs of patients with RA differ from those of healthy individuals [37]. miRNAs that target T-cell co-inhibitory molecules, like programmed death 1 (PD-1), were downregulated in EVs from RA patients, so EVs from PBMCs carry a T-cell inhibitory potential in RA patients [37]. This might be a protective mechanism against RA inflammation or might correlate with T-cells exhaustion [37].

3.4. Peripheral T cells

T cells play a major role in RA pathogenesis. Firstly, they contribute in the activation of synovial macrophages and rheumatoid arthritis synovial fibroblasts (RASFs) [9]. Secondly, an imbalance between Th17 and Tregs in RA patients, which favors Th17-associated systemic inflammation, has been reported [38,39]. Several miRNA changes have been described in T cells of RA patients

miR-17 has been found increased in serum exosomes of RA patients, associating with a decline in Tregs proportion in peripheral T cells [40]. Recently, disturbed levels of miRNAs that belong to the miR17-92 cluster were correlated with altered analogy of different subsets of peripheral γδ T cells in RA patients [41]. As for miR-146a, it is increased in peripheral Th17 cells [42] and decreased in peripheral Tregs [43], both contributing in enhanced secretion of proinflammatory cytokines. In addition, miR-223 in overexpressed in peripheral naïve CD4+ T cells and downregulated in Th17 cells [44].

3.5. RASFs

In RA patients several epigenetic mechanisms transform synovial fibroblasts into RASFs, which have a more aggressive profile [40]. RASFs are characterized by reduced apoptosis, increased proliferation, migration and invasion, enhanced proinflammatory cytokine production and production of enzymes that erode bone matrix (e.g. MMPs). They also orchestrate the local invasion of several cells that result in tissue damage [42].

Alterations in miRNA expression are responsible for many aspects of RASFs activity [45]. Various intracellular pathways in RASFs appear to be affected [46] by changes in miRNA levels and the most prominent implicated pathways are those of Wnt [47,48], NF-κB [49–52], JAK/STAT [53,54] and TLRs [51,55]. Most of the disturbed miRNA levels lead to secretion of pro-inflammatory cytokines or MMPs, increased proliferation and survival of RASFs, while few alterations oppose to the inflammatory milieu and the subsequent tissue damage (Table 2). miR-124a [56–59], miR-126 [60–62], miR-146a [63–65], miR-152 [66–68], miR-155 [27,54,64,65]and miR-221 [48,64,69,70] are the most studied miRNAs in RASFs. However, several other miRNAs have been analyzed in RASFs, such as miR-10a [71], miR-20a [72,73], miR-22 [74], miR-23b [75], miR-29a [76], miR-30a [77], miR-137 [78], miR-143 [50,79], miR-188 [80], miR-192 [81], miR-199a [82], miR-222 (143, 145), miR-223 [83], miR-338 [84], miR-346 [85,86], miR-539 [87] and miR-650 [88].

Indirect mechanisms also lead in changes in the expression of miRNAs in RASFs. Hypermethylation of the miR-124a and miR-34a genes in RASFs results in diminished apoptosis of RASFs and enhanced TNFa production [56,89,90]. Attenuated DICER1 expression in RASFs results in generally diminished miRNA expression in RASFs [91]. Moreover, *Li* et al. (2018) showed that circular RNA hsa_circ_0001859 acts as a "sponge" of miR-204/211, reducing their levels and thus allowing the increase of the proinflammatory transcription factor ATF2 in inflamed synoviocytes [92]. In a recent study, GAPLINC, a long non-coding RNA, was found increased in RASFs and seems to act also like a “sponge” of miR-382 and miR-575, reducing their expression in RASFs [93].

To be mentioned, miRNA expression in RASF-derived exosomes is also disturbed in RA. Increased levels of miR-146a, miR-155, miR-323a and miR-1307 were recently detected in RASFs exosomes after stimulation with TNFa [91]. The results of these changes are, on the one hand, to ignite local inflammation and, on the other hand, to attenuate octeoclastogenesis.

3.6. Synovial tissue and synovial macrophages

Low miR-27a levels in inflamed synovium lead in increased production of MMPs, which disintegrate the cartilage matrix and allow RASFs to migrate and invade the cartilage [51]. In addition, decreased levels of miR-30a in inflamed synovial tissues are correlated with reduced apoptosis and enhanced autophagy of RASFs and synovial macrophages [94]. Low expression of miR-708 in synovial tissue of RA patients might amplify Wnt/β-catenin signaling and increase RASFs survival and migration [95]. Finally, high levels of resistin in synovial fluid and synovial tissues of RA patients provoke a drop in miR-206 expression in endothelial progenitor cells [96]. This drop leads in production of vascular endothelial growth factor that contributes in neovascularization.

The local activation of innate immunity plays a crucial role in the development and perpetuation of synovial inflammation. miR-let-7b ligation to Toll-like receptor 7 (TLR-7) contributes to the remodeling of naive myeloid cells into M1 macrophage provoking arthritis [97]. Additionally, miR-155 has been found overexpressed in macrophages in synovial fluid and synovial tissue in patients with RA [25] and is correlated with low levels of anti-inflammatory agents [25] and pro-apoptotic proteins [30]. Moreover, genetic silence of miR-155 gene led to resistance to arthritis development [25,29]. Thus, increased miR-155 in local macrophages enhances their survival and the cytokine production. As for miR-223, its levels are increased in synovial macrophages of RA patients [98,99]. On the one hand, miR-223 overexpression leads to increased pro-inflammatory cytokines secretion [98]. On the other hand, it has a negative impact on osteoclastogenesis *in vitro* and possibly attenuates bone erosion formation [99]. Fig. 1 depicts the main implications of miRNA altered expression in synovial macrophages, RASFs, PBMCs and peripheral T cells of patients with RA (Fig. 1).

3.7. Osteoblasts, osteoclasts, chondrocytes

The synovial microenvironment in RA carries the potential to alter bone metabolism [100] and miRNAs play a crucial role on that [48]. *Maeda* et al. (2017) discovered 12 miRNAs with disturbed levels in inflamed synovium that participate in bone metabolism, especially osteoblast and chondrocyte differentiation [48]. The main pathways that were found to be involved, were those of Wnt and bone morphogenetic protein (BMP). miR-133a, miR-145a and miR-204a were downregulated, positively affecting the osteogenic transcription factors Runt-related transcription factor 2 (RUNX2) and Osterix (Osx), most likely as a compensatory mechanism. Additionally, miR-221 levels were found elevated, possibly inhibiting osteoblastogenesis through targeting Dickkopf-related protein 2 (Dkk2).

Osteoblasts synthesize bone organic matrix, mineralize it and participate in transcellular communication. In patients with RA, osteopontin (OPN) has found to inhibit miR-129 expression and provoke IL-17 production from the osteoblasts [101]. miR-146a and miR-183 levels in osteoblasts from RA patients have been found disturbed but the significance of these findings for the bone metabolism remains to be elucidated [102].

Osteoclasts bear the role of bone resorption, both in normal bone and in inflammatory arthritis. On the one hand, miR-145 is elevated in PBMCs and synovium of RA patients favoring osteoclastogenesis [23]. On the other hand, synovial macrophages exhibit elevated miR-146a, which inhibits their differentiation to osteoclasts and subsequent bone loss [63,103], while increased miR-223 in RA synovium restricts

Table 2
Changes in miRNA levels in RASFs. The changes in miRNA levels in RASFs, as well as the suggested target mRNAs and the results of these changes in RASFs are summarized (**NA**: Not available data, **RASFs**: Rheumatoid Arthritis Synovial Fibroblasts, **TBX5**: T-box transcription factor 5, **IRAK**: Interleukin-1 receptor-associated kinase, **TAK1**: Transforming growth factor beta-activated kinase 1, **TAB**: TAK1/MAP3K7 binding protein, **BTRC**: Beta-transducin repeat containing, **TRAF**: Tumor necrosis factor receptor-associated factor, **TNFAIP-3**: Tumor Necrosis Factor α-induced protein 3, **TLR**: Toll-like Receptor, **TXNIP**: Thioredoxin-interacting protein, **ASK1**: Apoptosis signal-regulating kinase 1, **NF-κB**: Nuclear Factor kappa beta, **Cyr61**: Cysteine-rich angiogenic inducer 61, **IKK-α**: IκB kinase α, **FSTL**: Follistatin-like protein 1, **STAT**: Signal transducer and activator of transcription, **BAFF**: B-cell activating factor, **XIAP**: X-linked inhibitor of apoptosis protein, **CDK2**: Cyclin-dependent kinase 2, **MCP1**: Monocyte Chemoattractant Protein 1, **PIK3R2**: Phosphatidylinositol 3-kinase regulatory subunit 2, **CXCL12**: C-X-C Motif Chemokine Ligand 12, **SCDF1**: Stromal cell–derived factor 1, **IGF1R**: Insulin-like growth factor 1 receptor, **IGFBP5**: Insulin-like growth factor-binding protein 5, **MAPK**: Mitogen activated protein kinase, **SEMA3A**: Semaphorin-3A, **DNMT1**: DNA (cytosine-5)-methyltransferase 1, **ADAM10**: A Disintegrin and metalloproteinase domain-containing protein 10, **JAK**: Janus Kinase, **IKBKE**: IκB kinase ε, **CEMIP**: Cell migration-inducing and hyaluronan-binding protein, **RB1**: Retinoblastoma 1 gene, **ATF2**: Activating transcription factor 2, **SOX5**: SRY-related HMG-box 5, **ROBO1**: Roundabout 1, **Wnt**: Wingless/Integrated, **Dkk**: Dickkopf-related protein, BMP: Bone morphogenetic protein, **NFI-A**: Nuclear factor I-A, **IL-17RD**: Interleukin 17 receptor D, **NFAT5**: Nuclear factor of activated T-cells 5, **Btk**: Bruton's Tyrosine Kinase, **TTP**: tristetraprolin, **FZD8**: Frizzled 8, **SOCS**: Suppressor of cytokine signaling, **OPN**: Osteopontin, **AKT2**: Protein kinase B 2, **APC**: Adenomatous polyposis coli gene).

miRNA	Change	Target	Results in RASFs	Reference
miR-10a	Decline	TBX5, IRAK4, TAK1, BTRC	↑Proliferation, ↓apoptosis, ↑NF-κB mediated inflammation	[71,109]
miR-17	Decline	TRAF2	↑NF-κB mediated inflammation	[49]
miR-18a	Incline	TNFAIP-3	↑NF-κB mediated inflammation	[105]
miR-19	Incline	TLR2 pathway	↑Inflammation	[55,150]
miR-20a	Decline	TXNIP, ASK1	↑Inflammation	[72,73]
miR-21	Incline	NF-κB pathway	↑ Proliferation	[151]
miR-22	Decline	Cyr61	↑Proliferation, ↑pro-inflammatory cytokines	[74]
miR-23b	Decline	TAB2, TAB3, IKK-α	↑IL-17 mediated inflammation	[75]
miR-27a	Decline	FSTL1, NF-κB pathway, TR4 pathway	↑Migration, ↑MMPs	[51]
miR-29a	Decline	STAT3	↑ Proliferation, ↓apoptosis	[53,76]
miR-30a	Decline	BAFF	↑B cell survival	[77]
miR-34a*	Decline	XIAP	↓Apoptosis	[89]
miR-124a	Decline	CDK2, MCP1	↑ Proliferation, ↑chemotaxis	[56–59]
miR-125b	Incline	NF-κB pathway	↑NF-κB mediated inflammation	[52]
miR-126	Incline	PIK3R2	↑Proliferation, ↓ apoptosis, ↓ pro-inflammatory cytokines	[60–62]
miR-137	Decline	CXCL12	↑Proliferation, ↑migration, ↑ pro-inflammatory cytokines	[78]
miR-140	Decline	Sirtuin1, SCDF1	↑Proliferation, ↓apoptosis, ↑migration	[142]
miR-143	Incline	IGF1R, IGFBP5, Ras/p38 MAPK	↑Proliferation, ↓apoptosis, ↑NF-κB mediated inflammation	[50,79]
miR-145	Incline	SEMA3A	↑Survival, ↑migration	[50]
miR-146a	Incline	IRAK-1? TRAF6?	NA	[63–65]
miR-152	Decline	DNMT1, ADAM10	↑ Proliferation, ↓apoptosis	[66–68]
miR-155	Incline	JAK2/STAT3, IKBKE	↓IL-6 mediated inflammation, ↓proliferation, ↓invasion, ↓MMPs	[27,54,64,65]
miR-188	Decline	CEMIP	↑Migration, ↑invasion	[80]
miR-192	Decline	Caveolin 1	↑ Proliferation, ↓apoptosis	[81]
miR-199a	Decline	RB1	↑ Proliferation, ↓apoptosis	[82]
miR-203	Incline	NF-κB pathway	↑IL-6 mediated inflammation, ↑MMPs	[56,106]
miR-204	Decline	ATF2	↑ Inflammation	[92]
miR-211	Decline	ATF2	↑ Inflammation	[92]
miR-212	Decline	SOX5	↑ Proliferation, ↓apoptosis	[124]
miR-218	NA	ROBO1, Wnt/β-catenin	↑Osteoblastic differentiation of RASFs	[47]
miR-221	Incline	Wnt (Dkk2), BMP	↓Osteoblastogenesis, ↓mineralization, ↓apoptosis, ↑pro-inflammatory cytokines	[48,64,70]
miR-222	Incline	Wnt/cadherin	↓Osteoblastogenesis, ↑proliferation, ↑neovascularization	[64]
miR-223	Incline	NFI-A, IL-17RD	↓Osteoclastogenesis, ↑ pro-inflammatory cytokines	[83,99]
miR-323	Incline	Wnt/cadherin	NA	[64]
miR-338	Incline	NFAT5	↑Proliferation, ↑migration, ↑invasion	[84]
miR-346	Incline	Btk, TTP	↓ Pro-inflammatory cytokines	[85,86]
miR-375	Decline	FZD8/Wnt	↑Inflammation	[152]
miR-522	Incline	SOCS3	↑ Pro-inflammatory cytokines, ↑MMPs	[107]
miR-539	Decline	OPN	↑Proliferation	[87]
miR-650	Decline	AKT2	↑Proliferation, ↓apoptosis, ↑migration	[88]
miR-663	Incline	APC	↑Proliferation, ↑MMP, ↑NF-κB mediated inflammation	[108]

osteoclastogenesis *in vitro* [99].

Some miRNAs contribute in MMPs production. MMPs support RASFs migration and dissolve the bone matrix, having, therefore, an important role in the pathogenesis of bone erosions [104]. In RASFs, elevation of miR-18 [105], miR-203 [56,106], miR-221 [70], miR-522 [107], miR-663 [108], and fall of miR-10 [109], miR-17 [49], miR-27a [51] and miR-375 [108] leads in increased secretion of several MMPs (MMP-1, MMP-2, MMP-3, MMP-9, MMP-13). In contrary, elevated miR-155 levels in RASFs might suppress MMPs production [27,65].

Synovial cartilage is metabolic active in RA. External and internal parameters configure the epigenetic landscape that influences chondrogenesis [110]. miR-23a has been found to be diminished in the cartilage of RA-affected joints [111]. This change seems to participate in NF-κB pathway activation, igniting the local inflammation, but also leads in increased MMP production. Moreover, miR-145a is diminished in RA synovial tissues and this decrease has been associated with chondrocyte differentiation, implying that miR-145a level fall might serve a compensatory role against cartilage loss [48].

4. The role of miRNAs in diagnosis, monitoring and treatment of RA

4.1. Contribution in diagnosis

Finding positive RF or ACPAs in serum is not sufficient for RA diagnosis. On the one hand, many healthy individuals are positive for these autoantibodies. On the other hand, a proportion of RA patients suffer from the seronegative form of the disease. Moreover, in daily clinical practice many patients with arthritis do not fulfill the diagnostic criteria for RA. On this basis, many studies have assessed miRNAs as

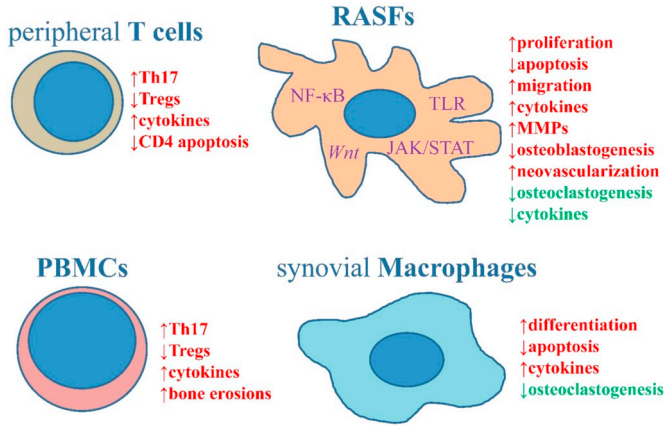

Fig. 1. The results of altered miRNA expression in RASFs, synovial macrophages, PBMCs and peripheral T cells of patients with RA (**Legend**: **RASFs**: rheumatoid arthritis synovial fibroblasts, **PBMCs**: peripheral blood mononuclear cells, **Th17**: T-helper 17 cells, **Tregs**: T-regulatory cells, **MMPs**: matrix metalloproteinases, **NF-κB**: nuclear factor kappa beta, **TLR**: toll-like receptor, **JAK/STAT**: Janus kinase/signal transducer and activator of transcription proteins, **CD4**: cluster of differentiation 4, **Wnt**: Wingless/Integrated).

Table 3
Serum miRNAs. The changes of serum miRNA levels in RA patients are presented as compared to healthy individuals.

miRNA	Change	Reference
miR-9	Decline	[73]
miR-10a	Decline	[77]
miR-15a	Incline	[75]
miR-24	Incline	[74,75]
miR-26a, miR-26b	Incline	[20,75]
miR-27a	Decline	[64]
miR-29a	Decline	[78]
miR-103a	Incline	[20]
miR-122	Decline	[73]
miR-124	Decline	[79]
miR-125a	Incline	[74,75]
miR-125b	Incline/Decline	[31,84]
miR-126	Decline	[80]
miR-132	Decline	[118]
miR-143	Decline	[123]
miR-146a	Incline	[20,75,125]
miR-155	Incline	[20,75,76]]
miR-181d	Incline	[73]
miR-210	Decline	[76]
miR-212	Decline	[82]
miR-219-2	Decline	[73]
miR-221	Incline	[60]
miR-223	Incline	[75]
miR-342	Decline	[73]
miR-346	Decline	[20]
miR-448	Incline	[79]
miR-499	Incline	[125]
miR-548a	Decline	[32]
miR-551b	Incline	[79]
miR-3925	Decline	[73]
miR-3926	Decline	[73]
miR-4634	Incline	[73]
miR-4764	Incline	[73]
miR-5196	Incline	[126]

possible biomarkers for RA diagnosis [112]. Plethora of data indicates that levels of circulating miRNAs differ among RA patients and healthy subjects (Table 3). Nevertheless, in some studies miRNA levels could not distinguish patients with RA from patients with OA [113].

A crucial issue in patients with new-onset arthritis is whether arthritis will progress to RA or not. *Alivernini* et al. (2018) found that miR-214 and miR-346 were statistically significantly reduced in patients with undifferentiated arthritis who later developed inflammatory arthritis that met seronegative RA or seronegative peripheral spondyloarthropathy criteria [114]. *Kurowska* et al. (2011) studied patients with early undifferentiated arthritis for 4 years and found significantly elevated levels of miR-371b, miR-483, miR-642b and decreased levels of miR-25 and miR-378d in the peripheral monocytes of the patients who eventually developed RA [25]. As mentioned above, miRNA expression differs depending on the stage of the disease. Lower miR-16 and miR-223 levels have been found in the peripheral blood of patients with early RA compared to healthy individuals and patients with long-standing disease [115]. Thus, serum miR-16, miR-25, miR-214, miR-223, miR-346, miR-371b, miR-378d, miR-483, miR-642b could contribute in early recognition of RA patients.

Analyzing concentrations of 1800 miRNAs in peripheral blood of treatment-naïve Chinese RA patients with active disease showed elevated levels of miR-181d, miR-4634 and miR-4764, while miR- 9, miR-122, miR-219-2, miR-342, miR-3925 and miR-3926 levels were reduced [116]. Four miRNAs, namely miR-122, miR-342, miR-3925 and miR-4764, managed to meet better diagnostic criteria for RA patients compared to healthy individuals, but also for patients with systemic lupus erythematosus (SLE) and Grave's disease. Additionally, comparing serum miRNAs from Japanese patients with RA, OA, SLE and healthy individuals, *Murata* et al. (2013) described statistically elevated levels of miR-24 and miR-125a in RA patients, regardless of the presence of positive RF and ACPAs or not [117]. The same group of researchers had demonstrated earlier that miR-132 is downregulated in the serum of RA patients but could not distinguish patients with RA from patients with OA [118].

In 168 RA patients from USA, serum miR-15a, miR-24, miR-26a, miR-125a, miR-146a, miR-155 andα miR-223 have been found elevated [119]. The greatest diagnostic accuracy for RA was found with the combination of increased miR-24, miR-26a and miR-125a and did not differ regarding RF and ACPA status. *Anaparti* et al. (2017) studied total plasma miRNA of Canadian patients with established seropositive RA and found increased levels of miR-26b, miR-103a, miR-146a and miR-155, as well as reduced levels of miR-346. In addition, in a study from Egypt, miR-155 was found to be elevated, whereas miR-210 was found to be reduced in RA patients' plasma compared to the healthy individuals [20,120].

In addition to the above-mentioned miRNAs, changes in the concentration of other miRNAs in RA patients' serum have been found. First of all, miR-10a [121], miR-27a [51], miR-29a [53], miR-124 [122], miR-126 [60], miR-143 [123] miR-152 [66] and miR-212 [124] have been found decreased, while miR-221 [70], miR-488 [122], miR-499 [125], miR-551b [122] and miR-5196 [126] have been found increased. Moreover, miR-548a has been found diminished in serum exosomes in RA patients [35]. In contrary, serum miR-210 levels failed to distinguish RA patients from healthy subjects [127]. Finally, regarding serum miR-125b and miR-146a in RA patients, no safe conclusions can be drawn at present due to conflicting reported results [20,34,52,119,128].

Conclusively, some changes in miRNA plasma concentrations could contribute in the diagnosis of RA. The strongest data available are for miR-24, miR-125a and miR-155, whose increase in the peripheral blood could be used to diagnose RA. Future studies need to focus on how serum miRNA levels could help in the differential diagnosis between RA and other arthritides.

4.2. Disease severity

Many studies reported that altered miRNA levels might reflect disease activity. *Murata* et al. (2013) showed that the more active the disease was, the higher the levels of circulating miR-24 were [117]. Few years earlier, the same team of researchers demonstrated that serum miR-16 levels were inversely proportional to DAS28 [118]. Low levels of miR-125b in PBMCs (but not in plasma) of treatment-naïve RA

patients have been associated with worse clinical picture [34]. *Pauley* et al. (2008) found that high levels of miR-16 and miR-146a in PBMCs of RA patients were associated with active disease, whereas low levels of these miRNAs were associated with remission of RA [22]. By studying miR-155 levels in PBMCs of patients with active disease, *Li* et al. (2013) found that the higher the miR-155 levels, the higher the ESR and the DAS28 were, irrespective of RF or ACPA presence [26]. Serum miR-155 levels have been also reported to correlate with disease activity [120]. On the contrary, *Filkova* et al. (2014) showed no correlation between miR-16, miR-132, miR-146 and miR-155 serum levels and clinical characteristics and inflammation markers in RA patients [128].

Additionally, patients with active RA had statistically increased serum levels of miR-194 and miR-432 and lower miR-210 levels than those in remission [122]. miR-221 and miR-222 levels in PBMCs have been found analogous to disease activity [31]. Moreover, the higher the levels of miR-223 in serum, of miR-451 in circulating T lymphocytes and of miR-522 in RASFs, the higher the activity of RA is [107,128,129]. To be mentioned, disease relapse has been associated with an increase in serum miR-223 levels [130]. Finally, studying blood samples from 76 patients with RA, *Wang* et al. (2018) found that lower levels of miR-548a in serum exosomes and PBMCs are correlated with more active disease [35]. Collectively, increased serum miR-223 levels have been associated with higher disease activity and disease relapse. Additional research is needed for other miRNAs to draw definite conclusions.

In some cases, RA is accompanied by various extra-articular manifestations. Patients with RA and interstitial lung disease (ILD) demonstrate increased serum miR-7 and miR-214 levels, compared to RA patients without lung involvement [131]. On the other hand, circulating miR-200 levels failed to distinguish RA patients with ILD from patients with ILD of a different origin [132]. When compared serum levels of six miRNAs among patients with RA with or without peripheral neuropathy, it was shown that those with peripheral neuropathy had statistically significant low levels of miR-9 [133].

4.3. Treatment response prediction

4.3.1. Conventional and targeted synthetic DMARDs

High pre-therapy serum levels of miR-16, miR-125b and miR-223 in patients with RA were associated with better response to therapy with non-biologic DMARDs, mainly with methotrexate [34,128]. Use of non-biologic DMARDs has also been shown to affect serum levels of other miRNAs, such as miR-10, miR-383 and miR-760 [130]; however, it is unknown whether these changes are correlated with disease activity

4.3.2. Anti-TNF and other biologic DMARDs

Several studies have examined the relation between serum miRNA levels and response to biologic DMARDs, either to TNF inhibitors (anti-TNF) or to others. Pre-therapy increased serum levels of miR-886 combined with low levels of miR-22 were highly predictive of response to treatment with adalimumab (ADA) after twelve months [134]. Likewise, RA patients with elevated serum miR-27a before initiation of ADA plus methotrexate combination were more likely to respond to this therapeutic regime, especially if miR-27a levels were diminished during the first 3 months of the treatment. In contrary, high baseline serum levels of miR-23 and miR-223 were inversely associated with response to anti-TNF agents [135]. Interestingly, "responders" (as defined by European League Against Rheumatism (EULAR) criteria, based on DAS28) exhibited an increase in miR-23 and miR-223 concentrations, while "non-responders" had a fall in these miRNAs levels after six months of treatment [135]. Additionally, after six months of anti-TNF treatment a drop in miR-5196 serum levels correlated with low DAS28 score. Finally, high baseline serum levels of miR-125b were predictive of clinical response to treatment with rituximab [136].

Anti-TNF agents and other biologic DMARDs use has been shown to increase the levels of miR-139, miR-204, miR-214 and miR-760 in peripheral T cells, though no data were available concerning clinical response (95). Two studies demonstrated an increase in serum miR-146a in patients under anti-TNF therapy without, however, exploring associations with the patients' clinical condition [15,135]. A study regarding the use of miR-99, miR-143 and miR-197 as predictive biomarkers to anti-TNF therapy failed to deliver consistent results [137].

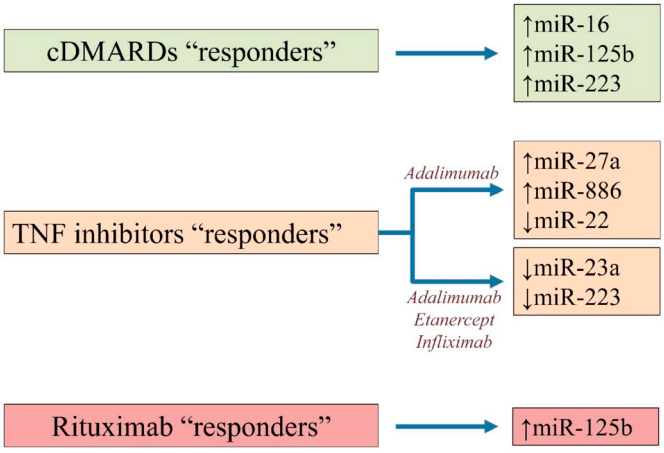

Fig. 2. Serum levels of specific miRNAs before treatment initiation could predict which patients will respond to the therapy. Response was defined by European League Against Rheumatism (EULAR) criteria, based on DAS28 **(Legend**: **TNF**: Tumor Necrosis Factor, **cDMARDs**: conventional disease modifying anti-rheumatic drugs, **DAS28**: Disease Activity Score 28).

In conclusion, current research on miRNAs as predictive biomarkers for treatment response in RA patients is very promising (Fig. 2). Specifically, baseline serum levels miR-16, miR-125b and miR-223 could serve as markers of therapeutic response for conventional DMARDs. As for biologic DMARDs, baseline serum levels miR-22, miR-23, miR-27a, miR-125b, miR-223 and miR-886 could be useful in predicting patient's response.

4.4. miRNAs as RA treatment

Interesting findings emerged from *in vitro* administration of specific miRNAs to RASFs. miR-26b mimic, increased apoptosis, diminished RASFs' proliferation and reduced cytokine production from RASFs [138]. miR-124a administration also decreased RASFs' proliferation, but also interferes with inflammatory cells chemotaxis [57]. Moreover, treatment of RASFs with miR-451 [139] or miR-573 [140] reduced RASFs' population, cytokine production and neovascularization.

In murine model of autoimmune arthritis, several routes of miRNAs administration have been used. Intra-articular (i.a.) injection of miR-15a, despite enhancing apoptosis locally, failed to improve arthritis [141]. In contrary, i.a. administration of miR-124 and miR-140 mimics, ameliorated arthritis severity, mainly through decreasing RASFs' population [58,142]. Intraperitoneal injection of miR-26a and miR-150 mimics, as well as miR-223 silencer, might also ameliorate arthritis [143]. miR-26a blocked TLR-3 pathway resulting in low cytokine secretion from macrophages [144], while miR-150 attenuated synovial hypertrophy and neovascularization [143]. miR-223 silencing ameliorated arthritis' severity, inhibited osteoclastogenesis and subsequent bone erosion formation [145]. Orbital injection of miR-106b inhibitor alleviated arthritis in mice with collagen-induced arthritis (CIA) through inflammation attenuation and bone loss prevention [146]. Intravenous administration of miR-146a and miR-708 mimics in mice with CIA was beneficial through prevention of synovial hyperplasia and structural joint damage [95,103]. Moreover, miR-34a antagonist suppressed cytokine production and inflammatory bone loss when it was administered intravenously [147]. Finally, 1,25-$(OH)_2$-vitD_3

administration in mice with CIA has been associated with lower miR-22 levels, decreased RASFs' proliferation and pro-inflammatory cytokine production [148].

5. Conclusions

miRNAs play a multi-faceted role in the context of RA development and are part of an extensive complex net of epigenetic interactions. Epigenetic alterations might be found either as a contributing factor in RA pathogenesis or as a result of the disease [149]. SNPs in specific miRNA genes (especially miR-499) expose individuals to increased risk for RA development or increased disease severity. Moreover, a plethora of miRNA alterations in several cells or tissues participate in RA pathophysiology or are consequent to disease process. This data unravels the deeper pathogenic mechanisms of systemic autoimmunity and local joint inflammation in RA and introduces a field for the discovery of new therapies. In addition, miRNA levels might allow early disease diagnosis, contribute in differential diagnosis or serve as biomarkers for predicting response to specific drugs that are used in RA treatment. Increased serum miR-22 and miR-103a might be used as prognostic markers for development of RA in individuals with positive ACPAs but without arthritis. Low serum miR-16 and miR-223 could help distinguish patients with ERA from healthy individuals. In patients with established RA, serum miR-24 and miR-125a are statistically significantly increased compared to healthy subjects, regardless of patient's RF and ACPA status. As for disease severity, increased serum miR-223 levels have been associated with higher disease activity and disease relapse. In RA patients that have developed ILD increased serum miR-7 and miR-214 levels have been found. Additionally, serum levels of miR-16, miR-22, miR-23, miR-27, miR-125b, miR-223 and miR-886 could serve as predictors of treatment response. Finally, several miRNAs have shown promising results as therapeutic factors in experimental models of arthritis, but their efficacy remains to be verified in clinical trials.

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Authors' contributions

GE: Collected literature, reviewed literature, drafted the manuscript. **GF**: Collected literature, reviewed literature, drafted the manuscript. **VK**: Collected literature, reviewed literature, drafted the manuscript. **GIL**: provided critical insight, proof-edited the manuscript and gave final permission for publication. All authors have read and approved the manuscript.

Declaration of Competing Interest

Nothing to declare.

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