Epigenetic regulation mediated by miRNA in the susceptibility and pathogenesis of rheumatoid arthritis

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Contribution:

micro-RNA (miRNA) has been demonstrated to play important roles in the transcriptome regulation and disease development including cancer and autoimmune disease such as rheumatoid arthritis. However, a comprehensive role of miRNAs in rheumatoid arthritis (RA) including immune system differentiation and interaction with terminal cells like T cells, fibroblast-like synoviocytes (FLS), osteoblast and osteoclast still unclear. In this review, we have provided a thorough summary on the roles of miRNAs in the susceptibility, pathogenesis, diagnosis, therapeutic intervention and prognosis. We summarized the blood and cell-free miRNA biomarkers which provided novel opportunity to work together with rheumatoid factors (RF), anti-CCP to provide accurate diagnosis and prognosis especially for seronegative patients. Finally, miRNAs were showed as promising biomarker to indicate the DMRDS and immunotherapy efficiency, drug response and resistance. What's more, autotherapeutic effect of miRNA intervention provided promising to develop miRNA based rheumatoid arthritis drugs. Overall, current evidence supports miRNAs as the interesting targets to better understand the pathogenetic mechanism and therapeutic intervention of rheumatoid arthritis.

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Abstract

micro-RNA (miRNA) has been demonstrated to play important roles in the transcriptome regulation and disease development including cancer and autoimmune disease such as rheumatoid arthritis. However, a comprehensive map on how the mRNAs regulate transcripts, pathways, immune system differentiation and interaction with terminal cells like T cells, fibroblast-like synoviocytes (FLS), osteoblast and osteoclast still unknown. In this review, we have provided a thorough summary on the roles of miRNAs in the susceptibility, pathogenesis, diagnosis, therapeutic intervention and prognosis. Numerous miRNAs were found abnormally expressed in rheumatoid arthritis relevant cells and regulated the target genes and pathways like *NF-κB*, *Fas-FasL*, *JAK-STAT*, *IRE1-RIDD, mTOR* pathway. In addition, miRNA act as gene expression regulators affect the T cell differentiate to different cell types including Th17 and T-reg cells which provide promising gene therapy target to regulate immune systems in rheumatoid arthritis. We also summarized interesting diagnosis and prognosis roles of blood and cell-free based miRNAs which provided novel opportunity to work together with rheumatoid factors (RF), anti-CCP to provide accurate diagnosis and prognosis especially for seronegative patients. Furthermore, functional genetic variants in *miR-499* and *miR-146a* explained part of missing susceptibility of rheumatoid arthritis. Finally, miRNAs were showed as promising biomarker to indicate the DMRDS and immunotherapy efficiency, drug response and resistance. What's more, autotherapeutic effect of miRNA intervention provided promising to develop miRNA based rheumatoid arthritis drugs. Overall, current evidence supports miRNAs as the interesting targets to better understand the pathogenetic mechanism and therapeutic intervention of rheumatoid arthritis.

Key words: rheumatoid arthritis, miRNA, susceptibility, pathogenesis, Epigenetics

Running title: Epigenetic regulation mediated by miRNA in Rheumatoid arthritis

Introduction:

Rheumatoid arthritis (RA) is an autoimmune disease with manifestation of chronic joint inflammation and structural damage and accompanied by extra-articular manifestations such as rheumatoid nodules, interstitial pneumonia, vasculitis, and systemic complications. Besides, it is usually progressive and insidious(1). However, currently, the underlying cause of RA's pathogenesis, disease activity, severity and difference in treatment effect are not fully understood. Under current rheumatoid arthritis therapy strategy and treatment frame, early accurate diagnosis and effective and personalized treatment and precision medicine have become the urgent problems for RA which required further and comprehensive understanding of rheumatoid arthritis including from the angles of both genetics(2) (*HLA* and non-*HLA* variants) and epigenetics (DNA methylation(3, 4), microRNA(5, 6), lncRNA(7, 8) and histone modifications(9)).

miRNA is a small endogenous non-coding single-stranded RNA family with a length of about 22 nucleotides and is involved in the regulation of post-transcriptional gene expression. In recent years, more and more studies have found that miRNAs play an important role in a variety of cancer(10-14) and autoimmune diseases including RA, systemic lupus erythematosus (SLE)(15, 16), Sjogren's syndrome (SS)(17) and systemic sclerosis (SSc)(18). In this review, we systemically summarized the advance of the miRNA research in rheumatoid arthritis especially the relationship between the genetic variants, expression variations and susceptibility, pathogenesis of rheumatoid arthritis in different inflammation-related cells, inflammatory cytokines and inflammatory signaling pathways (**Figure 1**).

Genetic variations in miRNAs explained missing susceptibility of rheumatoid arthritis.

Genome-wide association studies have identified >100 genetic factors for RA. However, these reported genetic variants only explain <40% overall heritability of RA. Majority of the heritability is still missing which require to be identified with more studies with different approaches and populations. Association study to miRNA locus provided an opportunity to identify RA associated functional or causal variants within different population Chinese(19, 20), Egyptians(21-23), Polish(24), Mexican(25), and Iranians(26). rs3746444 (20q11.22, A>G) in *miR-499* and intron of *MYH7B* was demonstrated to be significantly linked to RA risk, disease activity, and methotrexate toxicity(27) in which The AA genotype had higher disease activity and methotrexate toxicity compared with AG/GG genotypes(28). In addition, gene expression and genetic polymorphisms of *miR-146a* and *miR-499* showed diagnostic potentials for rheumatoid arthritis(23). rs2910164 in *miR-146a* was identified to be associated with RA susceptibility in the Egyptian population, in which C allele was protective(23, 28). rs3027898 in *IRAK1* which is the target gene of *miR-146a* was demonstrated associated RA in Greece population(29). However, follow-up studies showed inconsistent result in Poland(24), Mexico(25) and China(19, 20, 30, 31) population. SNPs located in other miRNAs were also tested in some studies however the association is not quite significant. For example, *miR-196a-2* (rs11614913C/T) and *miR-499* (rs3746444A/G) were showed do not have significant association with RA in Mexico population(25). *miR-146a* (rs2910164)(20, 31) and *miR-499* (rs3746444)(20, 30) were found do not have significant association with RA in Chinese. In our recent study, we found meta-analysis could identify more significant SNPs with large samples size and we found the interaction between HLA alleles and miRNA SNPs (rs5997893 in *miR-3928* and rs4947332 in *HLA-DRB1*) should be paid further attention to explain unmet susceptibility(32).

Gene and signaling pathways regulated by miRNA in the development of rheumatoid arthritis.

The cells involved in the pathogenesis of RA include $CD4^+$ T cells such as Th1, T-reg and Th17 cells, FLS, osteoclasts, and macrophages. The current research mainly focusing to identify miRNAs mediated transcriptional regulation to *FAF1*(33), *TNF*-α(34, 35), *STAT1*(36), *STAT3*(37), *TLR4*(38) and *mTOR*(39, 40). Therefore, the miRNAs receive the regulatory roles to inflammation, immune response, proliferation, differentiation and environment involvement within synovial joints mediated by above mentioned genes and related pathways including *Fas-FasL* pathway(33) and *NF-κB* pathway(34, 41, 42). In this section, we summarized the miRNA mediated regulation roles in the main RA associated cell entities including T cells, FLS, osteoclasts to explain the importance of miRNAs in the pathogenesis of RA.

miRNAs mediated innate and adaptive immune cell differentiation in rheumatoid arthritis

The balance of T-reg/Th17 cells plays an important role in RA. *IL-17* produced by Th17, which up-regulates Receptor Activator of Nuclear Factor-κB Ligand (*RANKL*), expression on synovial fibroblasts and induces innate immune cells to produce inflammatory cytokines such as *TNF-α*, *IL-6* and *IL-1*(43). The regulatory roles of *miR-146a* were widely studied in T cells and the evidence showed *miR-146a* was significantly increased in $CD4^+$ T cells, PBMC and Jurkat T cells, promoting T cell differentiation and inhibiting apoptosis(33, 44). Interestingly, the expression of *miR-146a* reduced in T-reg cells during high activity of RA, by targeting *STAT1*, resulting the proinflammatory phenotype of T-reg cells(36). Besides that, the high level of *miR-99b-5p*(40), *miR-361-5p*(45) and *miR-17*(46) participated in enhancing T cell proliferation and differentiation, anti-apoptosis. *miR-99b-5p* in peripheral blood mononuclear cells (PBMCs) was found to decrease the expression of mTOR and *RASSF4* genes to inhibit T cell apoptosis, promoted T cell proliferation and inflammatory response(40). Upregulation of *miR-17* in RA exosomes could inhibit the differentiation of T-reg by inhibiting the expression of *TGFB2*(46). *miR-21* decreased in peripheral blood circulating PBMCs(47), while increased in Vγ9Vδ2T cells(48) in RA patients, which associated with the imbalance of Th17/T-reg cells. *miR-120* negative regulation of *HIF-1* affects the dynamic equilibrium of Th17/T-reg cells.

Unfortunately, there was no association was found for *miR-120* in RA(49). In addition to inducing T cell differentiation, DNA methylation induced by miRNA plays an important role in the pathogenesis of RA. *miR-126* inhibited the methylation of promoter region in CD70 and CD11a to promote the expression of CD11a and CD70(50). The binding of *miR-6089* and *lncRNA-HIX003209* promoted the expression of *TLR4* and exacerbates inflammation through the *TLR4*/NF-κB pathway in macrophages(51). *miR-30a* could increase inflammation by aggravating autophagy and reducing apoptosis(52). Over-expression of *miR-192-5p* improves inflammatory response in RA by targeting up-regulation of Ras-related C3 botulinum toxin substrate 2 (*RAC2*)(53). Increasing the expression of *miR-20* and *miR-211* would subsequently down-regulate *ATF2*, thereby reducing inflammation in RA(54). The decreased expression of *miR-671*, *miR-96* in PBMC of RA patients may be related to the expression of *mTOR*(39) and endoplasmic reticulum stress induced by inositol-requiring enzyme 1 alpha (*IRE1*) / endoplasmic reticulum stress (*RIDD*) pathway(55). *miR-29b* enhances anti-apoptotic ability of PBMCs by inhibiting HMG-box transcription factor 1(*HBP1*) signaling(56). *miR-198*, *miR-4647* and *miR-7167-5p* were related to T cell signaling, apoptosis, immune response(57). There were numerous miRNA expression related to the T-reg subpopulation, *miR-21* and *miR-155* are related to the memory phenotype, while *miR-92a* is related to the naive phenotype(58). *miR-223* is highly expressed in naive $CD4^+$ T cell, but hardly expressed in Th17(59). Overexpression of *miR-361-5p* in early RA was associated with T cell activation and inflammatory response(45). These special expressions may be involved in the pathogenesis of RA, which deserve further research. Overall, miRNAs work together with DNA methylation and other non-coding RNAs (ncRNA) regulate the innate and adaptive immune cell differentiation, apoptosis, and then involved in the inflammation and autoimmune response in rheumatoid arthritis.

miRNAs mediated fibroblast-like synoviocytes and osteocyte differentiation in rheumatoid arthritis

Synovial fibroblasts are key regulators of inflammation and bone destruction in rheumatoid arthritis. In addition to produce *RANKL*, fibroblast-like synoviocytes in RA (C) also activates osteoclast differentiation by producing inflammatory cytokines, chemokines and matrix metalloproteinases (MMPs)(60). Large number evidence showed down-regulation of *miR-22*(61), *miR-29c-3p*(62), *miR-124a*(63), *miR-4701-5p*(8), and up-regultion of *miR-143*(64), *miR-145*(64) and *miR-191*(65) increased the proliferation, migration and invasion of RA-FLS. In contrast, down-regulation of *miR-132-3p*(62), *miR-29a*(37) and up-regulation of *miR-31-5p*(62) and *miR-124a*(66) inhibited the proliferation, migration and invasion of RA-FLS(62). *miR-199a-3p*(67), *miR-449a*(68), *miR-506*(38), and *miR-126*(35) are decreased in RA and targeted *RB1*, high-mobility group box protein 1 (*HMGB1*), *TLR4*, and *IL-23R*, and finally inhibited RA-FLS proliferation and induces apoptosis. The proliferation and invasion of RA-FLS is related to MMP(69). In RA-FLS, the up-regulation of *miR-145-5p*(41), *miR-18a*(34), *miR-155*(70, 71), *miR-203*(42), and the down-regulation of *miR-27a*(72) were participated in MMP expression through *NF-κB* pathway(34, 41, 42), *TLR4*(63), and Follistain like-1 (*FSTL1*) (72). *miR-625* was down-regulated in RA-FLS and negatively regulated *CTSC*, *KLF8*, *EBF3*. *miR-551b* was up-regulated in RA-FLS of RA and it down-regulated *ITGBL1*. *CTSC*, *KLF8*, *EBF3* and *ITGBL1* which are related to RA-FLS phenotype differentiation(73). In RA, bone loss is mainly due to overabsorption of bone by osteoclasts and weakened osteoblast bone formation(74). Overexpression of *miR-221-3p* inhibited osteoblast differentiation(75). *miR-218* overexpression inhibited the Roundabout 1(*ROBO1*)/Dickkopf-1 (*DKK1*) axis to promote osteogenic differentiation of RA-FLS(76).

Blood and serum-based miRNAs provided novel opportunity to the diagnosis of rheumatoid arthritis

The expression of *miR-371b*, *miR-483*, *miR-642b* is significantly up-regulated while *miR-25*, *miR-378d* are down-regulated in PBMC that eventually developed from early undifferentiated arthritis (EUA) into RA(77). Meanwhile, *miR-22*(78), *miR-361-5p*(45) and *miR-223-3p*(45) are significantly up-regulated in high-risk or CCP positive populations. Therefore, *miR-642b-5p*, *miR-483-3p*, *miR-371b-5p*, *miR-25-3p*, *miR-378d*, *miR-22*, *miR-361-5p* and *miR-223-3*p can be used as biomarkers for early diagnosis of RA. *miR-103a-3p* are

significant up-regulated in autoantibody-positive, asymptomatic first-degree relatives (FDR) and RA patients, indicates it can be a potential biomarker for predicting imminent disease in individuals at risk for developing RA(79). In addition, higher levels of *miR-143-3p*, *miR-145-5p*, *miR-99b-5p* are found in the plasma of early RA patients with bone erosion indicating the ability to be used for bone erosion surveillance in RA patients. Furthermore, *miR-99b-5p* was demonstrated to be an independent predictor of bone erosion progression in early RA(80). In addition to play role in early recognition of RA, the expression of some miRNAs aids to diagnose RA with higher accuracy(81). The expression of *miR-146a* and *miR-155* are significantly increased in RA PBMC, and there was a similar expression trend in whole blood(82). The expressions of *miR-24* and *miR-125a* are significantly up-regulated in the serum of RA patients regardless of CCP status(83). The combination of *miR-24-3p*, *miR-26a-5p* and *miR-125a-5p* showed better meet the diagnostic criteria of RA patients, However, they are not related to disease activities(84). *miR-122-3p*, *miR-3925-3p*, *miR-342-3p* and *miR-4764-5p* are differentially expressed not only in healthy individuals and RA patients, but also in RA patients and OA, SLE, and Graves patients(85). What's more, *miR-4634*, *miR-181d*, *miR-3926*, *miR-3926*, *miR-9-5p*, *miR-219-2-3p6*, *miR-221*, *miR-222*, *miR-532*, *miR-106a* and *miR-987* are also expressed differentially in the serum of RA patients which can be used as RA-specific diagnostic markers (85, 86).

The levels of *miR-146a*(87), *miR-22-3p*(88), *miR-5571-3p*(89) and *miR-135b-5p*(89) in the serum of the RA group are significantly higher than those in the healthy group and the OA group. In addition, the expression of *miR-451* in T cells of RA group is significantly increased, which is positively correlated with the levels of DAS28, ESR and serum *IL-6*(58). *miR-146a* is positively correlated with ESR and DAS28; *miR-5571-3p* is positively correlated with ESR and CRP and *miR-135b-5p* is positively correlated with CRP. Therefore, *miR-146a*, *miR-5571-3p*, *miR-135b-5p* and *miR-451* can be used as markers of disease activity in RA patients. In addition, an increase in serum *miR-194-5p* levels is associated with disease recurrence(90). The Serum expression of *miR-23b* which positively correlated with ESR, CRP and DAS28 are significantly up-regulated after treatment, indicating that *miR-23b* is a dual marker of disease activity and prognosis(91). *miR-96-5p*, *miR-134-5p*, *miR-140-3p*, *miR-627-5p* are not only diagnostic markers for RA, but also indicates the disease activity(92). In summary, the changes of miRNA in serum concentrations provided a promising opportunity for the early diagnosis, disease activity indicating and prediction of outcomes to RA.

Role of miRNAs in pharmacogenetics and therapeutic outcome and response prediction

The common and widely used anti-rheumatic drugs include cDMARD (Methotrexate, Sulfasalazine and Hydroxychloroquine), bDMARD (TNF inhibitors, Rituximab and Tocilizumab) and tsDMARD (Tofatinib, Barretinib and Flgotinib). Several studies have explored the relationship between serum miRNA levels and the response of DMARD. Evidence shows high serum levels of *miR-10* in RA patients is found related to the well response to MTX(93). After 3 months ADA/MTX combined treatment, serum level of *miR-27a-3p* is significantly decreased and the clinical symptoms of RA have remission(94). Serum level of *miR-5196* is significantly decreased in RA and AS patients after anti-TNF-α therapy and indicates a lower DAS28 scores(95). Meanwhile, serum level of *miR-146a* are showed decreased in RA patients who responded well to anti-TNF therapy and showed interesting response prediction ability to anti-TNF-α therapy(24, 96, 97) together with CRP. In contrast, serum level of *miR-23* and *miR-223* are increased in RA patients who response well to anti-TNF-α/DMARD combination therapy, while negative correlated to the response to anti-TNF drugs(96). High serum levels of *miR-125b* can be used to an indicator to well clinical response to Rituximab therapy(98). The expression of *miR-432-5p* decreased significantly in RA patients who are effective to tofacitinib therapy, but the expression of *miR-432-5p* increased in RA relapse patients(90). The treatment of Rituximab can increase the levels of *miR-16-5p* and *miR-23a-3p* in peripheral blood with RA(99). *miR-425-5p*, *miR-21-5p* and *miR-212-3p* are significantly decreased in RA patients treated with glucocorticoids, but no clinical response studies have been conducted(100). In addition to DMARD treatment, alternative and complementary medicine preparations and mesenchymal stem cell (MSC) treatments are

also used in the clinical treatment of RA. *miR-550b-2-5p*, *miR-4797-5p*, *miR-6509-5p*, *miR-378g*, *miR-4720-5p*, *miR-374b-5p* and *miR-185-3p* are showed differently expressed between individuals who have well and worse response to Tripterysium Glycosides (TG) treatment(101, 102). *miR-26b-5p*, *miR-487b-3p*, and *miR-495-3p* are up-regulated significantly in the responders with adipose-derived mesenchymal stem cell (eASCs) treatment(103). Furthermore, Geniposide treatment can increase the levels of *miR-124a* in FLS. However, the relevance with clinical response studies do mot conducted(104).

The auto therapeutic effect of miRNAs has been demonstrated in mouse models of RASF and autoimmune arthritis. *miR-506* mimics was showed to reduce the proliferation of RA-FLS and the production of pro-inflammatory cytokines. Meanwhile it can promote the apoptosis of RA-FLS(38). *miR-449a* mimics can inhibit proliferation, migration and *IL-6* production by regulating *HMGB1* and *YY1* expression in RA-FLS(68). In the autoimmune arthritis mouse model, the vein injection of *miR-708-5p* mimic showed improved pathological changes in CIA rat models including inhibit inflammatory cell infiltration, synovial hyperplasia and cartilage destruction(105). *miR-126* agonist can inhibit the expression of *IL-23R*, *TNF-α* and *IFN-γ* in the FLS of CIA rat model(35). MSC-derived *miR-124a* exosomes inhibit the proliferation and migration and promote the apoptosis of fibroblast-like synovial cell lines(66). In addition, *exo-miR-150* has been shown to inhibit RA - FLS proliferation and angiogenesis and reduce RA joint destruction by targeting *MMP14* and *VEGF* in rat *RASF* and CIA rat models(106). In conclusion, miRNA was demonstrated very important roles in the treatment of rheumatoid arthritis not only as the outcome biomarkers but also could be taken as novel drug target to decrease the severity of the patients of rheumatoid arthritis.

Challenge and opportunity of the current miRNA research in rheumatoid arthritis.

miRNAs play multiple roles in the development of RA from susceptibility and pathogenesis. As an important biomarker, blood and serum miRNA have been developed to different biomarkers for the early diagnosis and drug response prediction. Furthermore, miRNA has been proposed to be autotherapeutic approach and as the novel drug target for the treatment of rheumatoid arthritis. Genetic variants in specific miRNAs increase or decrease the risk and disease activity of RA in different ethnicity, and they are associated with methotrexate toxicity and other treatment response. In addition, the changes in miRNAs in various cells are related to the pathogenesis and pathological changes of RA, such as the proliferation and differentiation of immune cells, the proliferation and apoptosis of synovial cells, the synovial inflammation and cartilage destruction. Current research has received significant progress to develop miRNAs as the biomarkers for the diagnosis, prognosis, disease activity and the response to therapeutic drugs with RA, providing a direction for early diagnosis and accurate treatment of RA to receive better treatment efficiency and precision medicine. A variety of miRNAs have been shown to act as therapeutic targets in RA-FL and CIA rat models. miRNA also showed promising ability to identify subtypes of RA, for example, the expression levels of *miR-7* and *miR-214-5p* are significantly increased in the serum of RA-ILD patients(107) while *miR-9-5p* targeted *REST/miR-132* pathway to protects Schwann cells from inflammatory damage in RA-induced peripheral neuropathy(108). Although we have achieved exciting progress to investigate the multiple roles of miRNA in RA, more relevant studies should be implemented to understand and transfer current knowledge into the clinical application and solve the current inconsistent result among different studies with different method or populations. For example, Studies of *miR-99*, *miR-143* and *miR-197* as the landmark miRNAs for prediction to response to anti-TNF-α therapy have failed to yield results consistent with previous studies(109). Finally, we expect miRNA-based baseline rheumatoid arthritis polygenetic risk score model especially work together with HLA. Meanwhile, we miRNA based early diagnosis, prognosis and drug response prediction models could be applied in the future clinical application and miRNA based autotherapeutic treatment could show more promising result and more miRNA-based drug target could be identified in the further clinical research.

Author contributions

SG, DH conceived of content. SG, CC and LX drafted the review, which was edited by RZ, YJ and MX.

Competing interests

No potential conflicts of interest was disclosed for all the authors

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Figure Legends:

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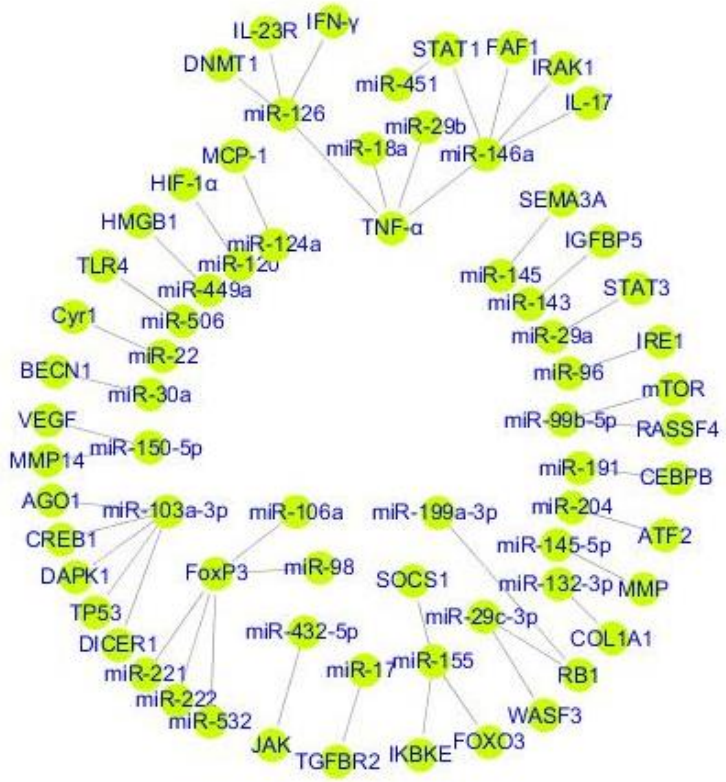

Figure 1. miRNA based regulatory network in rheumatoid arthritis. We extract all the regulatory network from the included studies and constructed the regulator network based on cytoscape. We can find numerous studies are focusing on TNF-a and cytokines while some other studies focusing on epigenetic regulation and inflammatory pathways.