Review

miRNAs and related polymorphisms in rheumatoid arthritis susceptibility

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The epigenetic mechanisms in regulation of genes’ expression seem to be another field of research that gains land in genetic association studies of rheumatoid arthritis (RA) susceptibility factors. Recently, a new class of molecules has been discovered, the microRNAs (miRNAs). miRNAs are related to post-transcriptional regulation of genes’ expression. Different expression patterns of mir-146a, miRNA-155, miRNA-124a, mir-203, mir-223, mir-346, mir-132, mir-363, mir-498, mir-15a, and mir-16 were documented in several tissue sample types of RA patients. The polymorphisms of these miRNAs and their gene targets, which previously have been associated with RA or other autoimmune diseases, are also reviewed. Finally, using web-based tools we propose polymorphisms of the discussed miRNAs and their gene-targets that worth to be studied for their role in RA predisposition.

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1. General overview

Rheumatoid arthritis (RA) is a chronic inflammatory disorder in which hypertrophy, hyperplasia and angiogenesis of synovial tissue contribute to inflammatory joint destruction [1,2]. Both genetic and environmental factors have been implicated in RA susceptibility [3]. The main genetic factor for RA is the HLA-DRB1 gene but the HLA (human leukocyte antigen) genes account only for the one third of the genetic liability to the disease [4]. Therefore, in the recent years many other non-HLA genes have been implicated in disease susceptibility but many other genes remain to be discovered [5].

The heritable changes in gene expression patterns that are not caused by changes in the primary DNA sequence, known as epigenetic regulation of gene expression, are revealed as another field of genetic factors associated with RA susceptibility [6–8]. Specifically, the epigenetic way of gene expression includes DNA methylation, histone modification, and transcriptional/post-transcriptional regulation of genes’ expression by non-coding small RNAs. DNA methylation, which occurs in cytosine bases of CpG islands, represses gene expression by decreasing the affinity of transcription factors’ binding or by recruiting MBPs proteins (methyl-CpG-binding) to the promoter region of gene sequence where they associate with co-repressors and impair transcriptional process [9,10]. Histone modification includes acetylation, methylation, phosphorylation, ubiquitylation, sumoylation, adenosine diphosphate ribosylation, deamination, and proline isomerisation which determine chromatin packing and as a result the transcriptional output [11]. Finally, the small non-coding RNAs are transcripts that are not translated into protein and mediate in transcriptional and post-transcriptional regulation of gene expression [12].

Recently, a new class of small non-coding RNAs have been identified, the microRNAs (miRNAs). miRNAs are small about 22 nucleotides in length and control the post-transcriptional regulation of up to 30% of all human genes [13]. Specifically, miRNAs act by binding mainly to the 3'-untranslated region of specific mRNA (message RNAs) targeting them for degradation or translation repression [14]. However, there are also studies which report that miRNAs might also interact with sequences in the 5'UTR, promoter or even in the coding regions of their target genes [15–17].

The majority of miRNA genes are mapped in introns and approximately the one third in intergenic regions [18]. In a first step, the miRNA is transcribed by RNA polymerase II leading to the primary miRNA hairpin structure. Subsequently, pri-miRNA is cleaved by the RNome enzyme Drosha together with its partner DGCRR8 (DiGeorge critical region 8) into the pre-miRNA. Then, pre-miRNA is exported by exportin 5 and its RAN-CTP (RAs-related nuclear protein -Guanosine-5'-triphosphate) cofactor into the cytoplasm, where it is further digested by Dicer (an RNaseIII enzyme) and its partner TRBP (transactivator RNA binding protein) into the mature double-stranded miRNA. Subsequently, miRNA is associated with RISC (RNA-induced silencing complex) and the separation of the two miRNAs strands occurs. The passenger strand usually is degraded while the leading strand and RISC bind to their gene target site cleaving the mRNA (in rare cases) or blocking its translation [18,19] (Fig. 1).

Abnormalities in miRNAs’ expression levels have been implicated to autoimmune diseases’ susceptibility and therefore, miRNAs could be used as potentially diagnostic or prognostic biomarkers and diseases’ therapeutic drug targets [20–22]. The aim of the present study is to review miRNAs that are expressed differentially in tissues of RA patients. Furthermore, we reviewed the reported polymorphisms of these miRNAs and their gene targets that have been associated with autoimmune and other human diseases and could be further examined in RA genetic association susceptibility studies. In addition, we used bioinformatics tools in order to identify other non-studied polymorphisms in miRNAs that were reported to be expressed differentially in RA patients and variants of these miRNAs gene targets aiming to shed light in the future genetic association studies.

2. miRNAs and related polymorphisms in RA

2.1. mir-146a

Increased expression of miRNA-146a has been documented in fibroblast-like synoviocytes (FLS), synovial fluid (SF), CD4 + T cells (lymphocytes positive for the CD4 phenotypic marker) from peripheral blood and synovial fluid, peripheral blood mononuclear cells (PBMC), and in serum plasma [23–28]. Furthermore, in RA patients miRNA-146a levels in synovial fluid were lower than those of their plasma [27].

Two known gene targets of miR-146a are the TNF receptor- associated factor 6 (TRAF6) and the interleukin-1 receptor-associated kinase 1 (IRAK1) [23,29]. Even though no significant difference in the miRNA or protein levels of TRAF6 and IRAK1 were observed between RA patients and control subjects, the repression of TRAF6 and/or IRAK1 in THP-1 cells resulted in TNFα reduced levels [23]. Therefore, it seems that the up-regulation of mir-146a expression may results in prolonged TNFα production through the deregulated expression levels of TRAF6/IRAK1, which are key adapter molecules downstream of the Toll-like and cytokine receptor signalling pathway [23,29]. In addition, IRAK2, FADD, IRF-5, Stat-1, PTC1, FAP1 genes were also suggested as mir-146a targets, a miRNA related to inflammation and apoptosis processes [26,29–33].

Up today, polymorphism mir-146a rs2910164 was mainly studied for its association with several diseases. Positive association of this variant was identified with cervical cancer, gastric cancer, cervical squamous cell carcinoma, esophageal squamous cell carcinoma, prostate cancer, papillary thyroid carcinoma, hepatocellular carcinoma, while the data for its association with breast or ovarian carcinoma are contradictory [32,34–45]. Specifically, polymorphism rs2910164 involves a G→C nucleotide substitution which causes change from a G:U pair to a C:U mismatch in the stem structure of mir-146a precursor. This variant was revealed to affect expression levels of mir-146a [32,35,42–44]. In addition, rs2910164 was associated with an additional generation of mature miRNA from the passenger strand (miR-146a*G and miR-146a*C) of the precursor miRNA in GC carriers. This fact can be of great importance due to the probable different selection of targets of the generated miRNAs [43].

Furthermore, we previously reported the positive association of IRAK1 rs3027898 A>G polymorphism with RA, ankylosing spondylitis (AS), and psoriatic arthritis (PsA) susceptibility [46,47]. This variant does not reside into a mir-146a target site, even though IRAK1 gene is a known target of this miRNA. However, it may affect the correct folding of the 3'-UTR of IRAK1 mRNA or may be in linkage disequilibrium with another not yet defined variant occurring in an IRAK1 target sequence of mir-146a. Both possibilities may disrupt eventually the post-transcriptional IRAK1 regulation and its role in Toll-like and cytokine receptor signalling pathway. It is worth mentioning that in the same studies we failed to find any association of mir-146a rs2910164 G>C variant with RA, PsA, or AS predisposition [46,47].

Finally, polymorphism rs6854081 of the fibroblast growth factor 2 (FGF2) gene, which is a predicted miRNA-146a target site, was significantly associated with femoral neck bone mineral density [48].

2.2. mir-155

Increased levels of miRNA-155, which is implicated in inflammation, antiviral immunity and remodelling pathways, have been revealed in synovial tissue (ST), FLS, SF, PBMC, and serum plasma [23,25,27]. Proposed targets of mir-155 are the genes MMP-1, MMP-3, c-Maf, Bach-1, PL1, CEBP, SHIP-1, ZIC3, HIVEP2, ZNF652, ARID2, SMAD5 [25,49,50].

The polymorphism rs5186 (also known as 1166A>C) in the 3'-UTR of AGTR1 (angiotensin II type-1 receptor) gene has been associated with deregulated expression of AGTR1 protein. Specifically, in the rs5186 C allele the base-pairing complementarity with the
recognition sequence of the miR-155 is interrupted. As a result, AGTR1 protein levels are increased in carriers of this allele [51–53]. Taking into account that AGTR1 protein was positively correlated with systolic and diastolic blood pressure, this fact supports the positive association of this polymorphism with hypertension [51–53].

2.3. miRNA-124a

Decreased levels of miRNA-124a were revealed in FLS. mir-124a was related to apoptosis and inflammation and its targets seems to be the genes CDK-2, MCP-1, and IκBζ [54,55].

2.4. mir-203

Increased expression of mir-203 was observed in FLS leading to their activation probably through the increased expression of MMP-1 and IL-6 via the NF-κB pathway [56].

2.5. mir-223

Higher expression levels of mir-223 were revealed in ST, FLS, SF, serum plasma, and CD4+ T cells from peripheral blood [57]. mir-223 levels in RA patients were lower in synovial fluid than these of their plasma [27]. This miRNA seems to affect granulopoiesis and glucose metabolism through E2F1 and CEBP genes [58, 59].

2.6. mir-346

Another miRNA, which was found increased in lipopolysaccharide treated FLS, is mir-346 [60]. mir-346 seems to be implicated in inflammation, hormonal and metabolism processes by targeting genes Btk and RIP140 [60,61].

2.7. mir-132, mir-363, mir-498

mir-132, mir-363, mir-498 have been associated with inflammation and neurotransmission [59,62,63]. Their gene targets have not
been defined and their levels are either increased or decreased depending on the tissue sample examined.

Specifically, mir-132 was up-regulated in ST, SF, PBMC and down-regulated in serum plasma [23, 27]. Additionally, mir-132 levels were lower in synovial fluid than those of plasma in RA patients [27].

mir-363 was decreased in CD4 + T cells from joint or blood but increased in PBMC [26].
mir-498 was down-regulated in CD4 + T cells from synovial fluid or peripheral blood [26].

2.8. mir-15a, mir-16

mir-15a was found increased in ST, while mir-16 was up-regulated in ST, SF, PBMC and serum plasma [23, 27]. mir-15a and mir-16 affect apoptosis and proliferation through a variety of gene targets [BCL2, DLK1, PDCD4, TIA1, RASSF5, Bim-1, Cyclin D1, cyclin E1, MYBA] [64–70].

Chromosome 13q14 deletion, where mir-15a/16 cluster is mapped, has been associated with spindle cell lipomas, conventional lipomas, and chronic lymphocytic leukaemia [71–74]. It is worth mentioning, that the biallelic deletion has mainly been associated with significantly lower miRNA expression of the mir15a/16 cluster [72, 74].

3. Searching for polymorphisms associated with RA

Today, many single nucleotide polymorphisms (SNPs) in 3'–UTRs are known to alter the binding of a miRNA to its gene target causing several human diseases [75]. For this reason many web-based tools are now available for the prediction of miRNAs' gene targets and for the identification of SNPs located in such 3'–UTR sequences. Since the interplay between SNPs and miRNAs is important, prediction of SNPs that could alter the expression of a miRNA or its complementarity with the gene target, and as a result the normal function of the involved molecular pathway, seems to be of great importance.

Specifically, and first of all, we used the web-site http://www.ma.uni-heidelberg.de/apps/zmf/mirwalk in order to identify in which of the aforementioned pairs of miRNAs-gene targets the computational tools do predict such an interplay among them. The analysis was carried out determining the following defaults: a) the longest mRNA transcript, b) selected gene regions were the promoter, 3'–UTR, 5'–UTR, and the coding regions, c) the minimum seed length was 7 nucleotides, and d) the selected prediction programmes were the mirWalk, miRANDA, miRDB, RNA22, and TargetScan. The results of this analysis are summarized in Table 1.

Subsequently, we used MicroSniper, a new web-based tool, which can predict if a SNP within the 3'–UTR of a gene is implicated in disruption/elimination or enhancement/creation of a miRNA binding site [76]. Specifically, we tested the aforementioned gene targets of each above discussed miRNA. It is true that we found many SNPs in the 3'–UTR of the studied target genes, which however were implicated in sequences recognised by other miRNAs and not by the miRNAs that were previously reported in the literature and were reviewed above. Only, polymorphisms rs11079869 G>A and rs12103812 G>A in the 3'–UTR of ZNF652 are mapped in sequences targeted by mir-155. Consequently, the study of these variants in RA susceptibility seems to have a priority.

Finally, using the web-based Patrocles database we identified only two SNPs in the coding sequences of the aforementioned miRNAs: the

<table>
<thead>
<tr>
<th>Table 1</th>
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<td>The predicted locations of the interplay among miRNAs that differentially expressed in RA patients and their reported gene targets.</td>
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</table>

*p-value: A probability distribution of random matches of a subsequence (miRNA 5' end sequence) in the given sequence (promoter or mRNA sequence), is calculated using Poisson distribution. A low probability implies a significant hit. (Sadygov, R.G et al., 2003; Havilio et al., 2003. By default P-value = 0.05 was selected), SPMS stands for the Starting Position of miRNA Seed Sequence.
known and widely studied miR-146a rs2910164 G>C polymorphism and the polymorphism rs34952239 (referred to a deletion of a C nucleotide) of the premature miR-223. This variant also seems to outweigh in RA genetic association studies.

4. Future perspectives

The target–prediction computational tools are based mainly on the complementarity between miRNA seed–gene target and the cross-species conservation of the seed. However, the complementarity between the miRNA and its target gene can be affected by the molecular structure of miRNAs and miRNA targets, other nearby genetic variants, while the prediction of the correct pair of a miRNA and its gene target for their study in a specific disease susceptibility can be affected by the expression patterns of miRNAs in different tissues and cells, the occurrence of miRNA targets also in the 5′-UTR and the coding regions of the target genes. Taking this into account, we realize the complexity to identify SNPs that truly affect the interplay among miRNA-mRNA and are related to diseases' predisposition. Consequently, it is not strange that a minority of computationally results are experimentally validated [77,78]. Therefore, the identification of more complex and sophisticated computational tools seems to be of critical importance in order to direct the selection of the critical SNPs and the future genetic association studies.

Conflict of interest

The authors have no conflict of interest to report.

Take-home messages

• There are miRNAs that are expressed differentially in tissues obtained from RA patients.

• Polymorphisms in these miRNAs or their genes targets that affect miRNA expression levels or the correct binding among miRNA–gene target could be associated with RA susceptibility.

• Web-based tools are now available to predict such polymorphisms that worth to be included in RA genetic association studies.

References


[18] Zou X, Duan X, Qian J, Li F. Abundant conserved microRNA target sites in the 5′-untranslated region and coding sequence. Genetica 2009;137:159–64.


[22] Zou X, Duan X, Qian J, Li F. Abundant conserved microRNA target sites in the 5′-untranslated region and coding sequence. Genetica 2009;137:159–64.

[23] Zou X, Duan X, Qian J, Li F. Abundant conserved microRNA target sites in the 5′-untranslated region and coding sequence. Genetica 2009;137:159–64.


[26] Zou X, Duan X, Qian J, Li F. Abundant conserved microRNA target sites in the 5′-untranslated region and coding sequence. Genetica 2009;137:159–64.

[27] Zou X, Duan X, Qian J, Li F. Abundant conserved microRNA target sites in the 5′-untranslated region and coding sequence. Genetica 2009;137:159–64.


[29] Zou X, Duan X, Qian J, Li F. Abundant conserved microRNA target sites in the 5′-untranslated region and coding sequence. Genetica 2009;137:159–64.


[31] Zou X, Duan X, Qian J, Li F. Abundant conserved microRNA target sites in the 5′-untranslated region and coding sequence. Genetica 2009;137:159–64.


[33] Zou X, Duan X, Qian J, Li F. Abundant conserved microRNA target sites in the 5′-untranslated region and coding sequence. Genetica 2009;137:159–64.

[34] Zou X, Duan X, Qian J, Li F. Abundant conserved microRNA target sites in the 5′-untranslated region and coding sequence. Genetica 2009;137:159–64.


[37] Zou X, Duan X, Qian J, Li F. Abundant conserved microRNA target sites in the 5′-untranslated region and coding sequence. Genetica 2009;137:159–64.
Autocrine TNF Is Critical for the Survival of Dendritic Cells by Regulating BAK, BCL-2, and FLIPL

The life span of dendritic cells (DCs) is determined by the balance of pro- and antiapoptotic proteins. In this study, Lehner M et al. (J Immunol 2012; 188(10): 4810–8) report that serum-free cultured human monocyte-derived DCs after TLR stimulation with polyinosinic:polycytidylic acid “cross-talk” with their microRNA-16 expression, which is decreased during differentiation. The authors show that this decrease in microRNA-16 expression correlates with an increase in BAK expression, leading to increased apoptosis. The authors suggest that this cross-talk between microRNA and protein expression is critical for the survival of DCs and may be a target for therapeutic intervention.

E. Toubi