microRNAs in rheumatoid arthritis: midget RNAs with a giant impact

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ABSTRACT

MicroRNAs (miRNAs) are tiny, non-coding molecules that primarily modulate gene expression at the post-transcriptional level by predominantly hybridising to complementary sequences in the 3'-untranslated region of their corresponding mRNAs. Depending on the degree of Watson-Crick base pairing, a miRNA either accelerates the degradation of the corresponding transcript or restricts its translation. There is compelling evidence that miRNAs have crucial roles in controlling and modulating immunity, while dysregulation of miRNAs can lead to autoimmunity and promote tumourigenesis, making miRNA regulation a balancing act between immunity and tumourigenesis. Here, the focus is on the role of miRNAs during the establishment and sustainment of rheumatoid arthritis (RA), a systemic, inflammatory autoimmune disease with irreversible joint destruction. An overview of the known function of miRNAs in RA and what the future might hold for the use of these small RNA molecules in RA diagnosis and treatment is provided.

Rheumatoid arthritis (RA) is a systemic, inflammatory autoimmune disease primarily characterised by irreversible destruction of affected joints. Since the first recognised description of RA in 1800 by Dr Augustin Jacob Landré-Beauvais,¹ much has been learnt about this disabling and painful condition. Approximately 1% of the world's population is afflicted by RA, with women being affected three times more often than men. Generally, the symptoms and signs of RA are diagnosed by x-ray or blood tests for rheumatoid factor, but the disease is not currently curable. Conventional non-pharmacological treatment of RA includes physical therapy, orthoses or occupational and nutritional therapy, while analgesia and anti-inflammatory drugs are used to suppress the symptoms of RA. In recent years, an enhanced understanding of the molecular pathogenesis of RA has enabled the development of innovative biological agents known as disease-modifying antirheumatic drugs. New therapeutic strategies that promote the early use of these drugs now allow the underlying immune process to be inhibited or prevented and long-term damage avoided, thereby permitting tight disease control and distinct and quantifiable treatment goals. These agents target specific parts of the immune system and yield significant improvement, changing the course and face of RA and the outcomes for patients. Although current treatments with biological agents such as tumour necrosis factor α (TNF α) blockers can halt most cases of joint destruction, not all instances of joint inflammation and associated conditions are cured by these treatments.

Even though it is known that persistent activation of the immune system in RA leads to autoimmunity, the trigger activating the immune response remains unclear. A complex interplay between the immune system, environmental factors and multiple genes contributes to disease susceptibility, with the human leucocyte antigen locus accounting for 30–50% of overall genetic risk. Therefore, understanding the biological principles of the cause and pathogenesis of RA and all its subsets will lead to better treatment regimens and disease prevention.

Promising research in this direction was the discovery of microRNAs (miRNAs), a class of endogenous 19–25-nucleotide long, non-coding RNA molecules. Single-stranded miRNAs interact with the RNA-induced silencing complex (RISC) and regulate a wide variety of other genes by either preventing the translation or inducing the cleavage of complementary messenger RNAs (mRNAs). Owing to the imperfect Watson-Crick pairing of a single-stranded miRNA with its corresponding complementary sequence, mostly found in the 3'-untranslated region (3'-UTR) of an mRNA, a single miRNA could have hundreds of mRNA targets.

First described in 1993 by the Ambros group, was lin-4, the first short, non-coding RNA that regulates the translation of the lin-7 mRNA.² Because lin-4 does not have a homologue in other species, this finding was thought to be specific to *Caenorhabditis elegans*. However, the discovery of the *C. elegans* miRNA let-7 with homologues in humans and other species in 2000 by the Ruvkun group established miRNAs as potent modulators of post-transcriptional regulation of gene expression.³ The biogenesis of a miRNA begins in the nucleus with the transcription of the respective miRNA gene (figure 1). The primary (pri-) miRNA transcript consists of a short, imperfectly base-paired, stem-loop structure that contains the sequence for the mature miRNA. The hairpin structure is released in the nucleus from the pri-miRNA as a ~70-nt-long precursor (pre-)miRNA by Drosha, a nuclear RNaseIII enzyme.⁴ Drosha is part of a miRNA processor complex that also contains the double-stranded RNA binding protein DGCR8 (also called Pasha (Partner of Drosha)).⁵ Because DGCR8 is essential for Drosha's activity on pri-mRNA and Drosha is also involved in the processing of ribosomal RNA,⁶ it was proposed that DGCR8 targets Drosha at its specific pri-miRNA cleavage site by also binding to single-stranded parts of the pri-miRNA.⁷

Pre-miRNAs are transported into the cytoplasm by exportin 5,^{8–10} where they are further processed by Dicer, a second RNaseIII enzyme that cuts off the terminal loop and generates an imperfect double-stranded RNA duplex that is about 22 nucleotides

Figure 1 Biogenesis and mechanism of action of microRNAs (miRNAs). After transcription by RNA polymerase II or III, the pri-miRNA hairpin structure is processed in the nucleus by the RNaseIII enzyme Drosha together with its partner DGCR8 into the pre-miRNA. After export into the cytoplasm by exportin 5, the pre-miRNA is processed by the second RNaseIII enzyme Dicer into the mature double-stranded miRNA that is about 22 nucleotides in length. Association with the RNA-induced silencing complex (RISC) leads to miRNA strand separation. The passenger strand is degraded and the leading strand and RISC bind predominantly to the 3'-UTR of mRNAs, leading either to the cleavage of target sites (in rare cases), the restriction of translation or the decapping and deadenylation of the mRNA.

in length. This duplex binds to proteins of the Argonaute family, which are part of the RISC. After unwinding the duplex and discarding the passenger strand, RISC is directed to its target mRNA by the single-stranded lead strand, which pairs to complementary sequences that are primarily located in the 3'-UTR of mRNAs. In the rare case of a perfect Watson-Crick base pairing, the target mRNA is cleaved by the RNase activity of Argonaute. However, a more common imperfect base pairing leads either to translational repression or to decapping and deadenylation (reviewed by Peters and Meister; Wu and Belasco; Stefani and Slack¹¹⁻¹³).

The imperfect base pairing of miRNAs makes mRNA target predictions difficult. Although several algorithms have been developed to aid the *in silico* identification of bona fide miRNA-controlled target mRNAs, their performances still need to be improved. Complicating things further, often one mRNA can be the target of several miRNAs, and vice versa, one miRNA can target up to several hundred mRNAs.

Much has been learnt about miRNAs since their discovery 17 years ago. An important role for these tiny molecules in development was inferred from their conservation and expression patterns in different tissues. Known functions of miRNAs in animals include timing developmental transitions, regulating cell proliferation and differentiation, fine-tuning fat and lipid metabolism and modulating insulin secretion. Therefore, it is not surprising that miRNA molecules also have important roles in diseases and cancers (reviewed by Esquela-Kerscher and Slack¹⁴). It is becoming increasingly clear that proper miRNA regulation is also critical for the prevention of autoimmunity and normal immune functions. However, it is not yet well understood whether miRNA dysregulation might have a role in the pathogenesis of autoimmune disease in humans. This review therefore focuses on the potential roles of miRNAs in the development and sustainment

of RA with an emphasis on the differential expression of several immunity-regulating miRNAs in patients with RA.

Intensive research in recent years, especially in the murine system, has uncovered crucial roles of several miRNAs in the establishment, maintenance and function of all haematopoietic lineages. Ectopic overexpression or silencing of miRNAs and knockout or transgenic animal models have contributed to the basic understanding of the functions of several known players, including miR-150, miR-155, miR-17~92, miR-181 and miR-223. Further information on haematopoietic miRNAs is available in excellent reviews such as the one by O'Connell *et al.*¹⁵

DEREGULATED miRNAs IN SYNOVIAL TISSUE AND CELLS OF PATIENTS WITH RA

The first clue of the role of RNA interference pathway factors in autoimmune disease was noted by Jakymiw *et al.*¹⁶ They reported that anti-Su autoantibodies from human patients with rheumatic diseases recognise several components of the RNA interference pathway, indicating that this autoantigen is part of the miRNA-processing machinery.

The first three miRNA studies using material from patients with RA were performed in 2008; these studies uncovered altered miRNA expression in patients with RA compared with controls.¹⁷⁻¹⁹ Stanczyk *et al.*¹⁷ investigated the expression, regulation and function of miR-146a and miR-155 in RA synovial fibroblasts (RASFs) and RA synovial tissue. Using microarrays, they reported increased miR-146a and miR-155 expression in RASFs compared with patients with osteoarthritis (OA).¹⁷ Additionally, miR-155 expression in RA synovial tissue was higher than in OA synovial tissue, as was the level of miR-155 in RA peripheral blood monocytes compared with RA synovial fluid (SF) monocytes. The levels of miR-155 were also markedly upregulated in RASFs following the addition of proinflammatory

stimuli, such as TNF α , interleukin (IL)-1 β and Toll-like receptor ligands, while only IL-1 β and lipopolysaccharide (LPS), but not TNF α , also induced the expression of miR-146a in RASFs. These results were consistent with the previously observed upregulation of miR-146a and miR-155 expression after LPS challenge in the human monocytic cell line THP-1.²⁰ Promoter analysis of the miR-146a gene showed that NF- κ B, a key regulator of RA inflammation, has a critical role in the induction of miR-146a transcription in response to LPS, TNF α and/or IL-1 β .²⁰

Matrix metalloproteinases (MMPs) are involved in the pathogenesis of RA through their proteolytic activities on joint or articular cartilage. It was therefore intriguing when Stanczyk *et al*¹⁷ noted that the forced expression of miR-155 in RASFs reduced the expression of MMP-3 and impaired the induction of MMP-1 and MMP-3 by Toll-like receptor ligands and cytokines, suggesting that the inflammatory milieu may alter miRNA expression profiles in resident cells of the rheumatoid joints. miR-155 may modulate downstream tissue damage or even have a protective function in RA by downregulating the expression of certain MMPs, thus alleviating tissue damage.

The second study that examined miRNA expression in RA synovial tissue and fibroblasts was conducted by Nakasa *et al*¹⁸, who investigated the expression pattern of miRNA-146a in synovial tissue from patients with RA and reported that miR-146a was highly expressed in RA synovial tissue compared with OA and normal synovial tissue. In situ hybridisation studies showed that miR-146a expression can be detected in cells of the superficial and sublining layers in RA synovial tissue, primarily in CD68-positive macrophages, but also in some CD3-positive T-cell subsets and CD79a-positive B cells.¹⁸ The expression of miR-146a was markedly induced in RASFs after stimulation with TNF α and IL-1 β .

The third of the initial miRNA-RA studies demonstrated that miRNA expression in peripheral blood mononuclear cells (PBMCs) from patients with RA mimics that of synovial tissue or fibroblasts.¹⁹ PBMCs from patients with RA or controls were analysed by real-time RT-PCR analysis for selected miRNAs. A differential expression of miRNAs was noted in RA PBMCs, with 1.8- to 2.6-fold increases in miR-16, miR-132, miR-146a and miR-155 expression, whereas miRNA let-7a expression was not significantly different from that of healthy controls. Interestingly, increased miR-16 and miR-146 expression correlated with active disease in patients with RA; however, there was no correlation between the observed increase in miRNA expression and the patients' age, race, or drugs. Two known targets of miR-146a, TNF receptor-associated factor 6 (TRAF6) and interleukin-1 receptor-associated kinase 1 (IRAK1), were examined, and despite increased miR-146a expression in patients with RA, there was no significant difference in the mRNA or protein levels of TRAF6 or IRAK1 between patients with RA and control subjects. In vitro studies have shown that the repression of TRAF6 and/or IRAK-1 in THP-1 cells results in up to 86% reduction in TNF α production, suggesting that normal miR-146a function could be critical for the regulation of TNF α synthesis. Given that prolonged TNF α production is known to have a role in RA pathogenesis, these data suggest a possible mechanism contributing to RA pathogenesis, where miR-146a expression is increased but unable to properly regulate TRAF6/IRAK1, thereby leading to prolonged TNF α production in patients with RA.

During the inflammatory phase of RA, the cytokine IL-18 is elevated in the synovium. A previous study by Zeisel *et al*²¹ showed that synoviocytes treated with LPS express IL-18 mRNA but do not release the IL-18 protein owing to an increased

degradation of the transcript. Recently, Alsaleh *et al*²² have reported an upregulation of miR-346 in LPS-treated RASFs using microarray and quantitative RT-PCR analyses. The suppression of miR-346 with an antisense oligonucleotide resulted in the release of IL-18 protein by indirectly inhibiting LPS-induced Bruton's tyrosine kinase expression, which is involved in the stabilisation of cytokine mRNAs. Therefore, miR-346 may function to fine-tune inflammatory processes in RA.

One possibility of interfering with miRNA function is the in vivo administration of chemically synthesised miRNAs. Nagata and colleagues have used an autoantibody-mediated arthritis mouse model to study whether intra-articularly injected miR-15a might be taken up by cells and might induce Bcl-2 dysfunction and cell apoptosis.²³ This proof-of-concept study was of interest, as miR-15a was reported to induce cell apoptosis by negatively regulating the expression of Bcl-2, which suppresses apoptotic processes.²⁴ Indeed, miR-15a expression in the synovium of the experimental group was significantly higher than that of the control group, while Bcl-2 protein was downregulated and the expression of caspase 3 was increased. This approach might be used as a novel therapeutic strategy to ectopically overexpress miRNAs with the desired cellular outcome in vivo by the intra-articular injection of miRNA into the joints.

Nakamachi and colleagues compared the miRNA expression profiles of synoviocytes from patients with RA and OA and demonstrated that miR-124a is significantly underexpressed in RA synoviocytes.²⁵ The transfection of precursor miR-124a into RA synoviocytes inhibited their proliferation and arrested the cell cycle at the G1 phase. This presumably occurs via binding to cyclin-dependent kinase 2 and monocyte chemoattractant protein 1 (MCP-1) mRNA, as they harbour predicted miR-124a binding sites and are specifically suppressed by the overexpression of miR-124a. MCP-1, which is also known as chemokine (C-C motif) receptor 2 (CCR2), is a highly expressed cytokine in synovial tissue and SF in patients with RA. Low levels of miR-124a could lead, via MCP-1, to the recruitment and retention of mononuclear phagocytes into the joints, thereby fuelling inflammation in RA.

DEREGULATED miRNAs OF T CELLS IN RA

A hallmark pathological feature of RA is the infiltration and accumulation of T cells in the synovium of the joints.²⁶ T cells isolated from SF and joint tissue show an activated and memory phenotype, appear to respond poorly to stimulation with mitogen or antigens in vitro and fail to undergo apoptosis.²⁷ The possible mechanism underlying the impaired apoptosis of T cells in RA remains largely unclear. The inhibition of T-cell death may therefore result in the persistence and accumulation of T cells in the synovium and in the accumulation of T cells in the periphery.

Findings by Yu and colleagues recently illuminated a critical post-transcriptional pathway within T cells that regulates lymphocyte accumulation and autoimmunity.²⁸ Inducible T-cell co-stimulator (ICOS)-deficient mice are resistant to collagen-induced arthritis and do not develop joint tissue inflammation. Interestingly, miR-101 was reported to regulate ICOS by targeting the 3'-UTR of ICOS mRNA, which highlights the therapeutic potential of partially antagonising the ICOS pathway and preventing autoimmunity by limiting the levels on T lymphocytes, possibly by the use of miRNAs.

A recent study by Li and colleagues investigated the expression pattern and function of miRNAs in CD4 T cells from the SF and peripheral blood of patients with RA.²⁹ These investigations

showed that miR-146a expression was significantly upregulated in the CD4 T cells of patients with RA, while miR-363 and miR-498 were downregulated. The abundance of miR-146a expression was positively correlated with that of TNF α , and in vitro studies have shown that TNF α induces the upregulation of miR-146a expression in T cells. Moreover, miR-146a overexpression was found to suppress T cell apoptosis by regulating Fas-associated factor 1, which is critically involved in modulating T-cell apoptosis. This finding indicates that miR-146a may be involved in maintaining inflammation during RA pathogenesis and could represent a potential novel therapeutic target.

A second study by Fulci and colleagues analysed miRNA expression in T lymphocytes from the peripheral blood of patients with RA and healthy controls. Their analysis showed that miR-223 is the only miRNA significantly upregulated in CD4 naive T lymphocytes.³⁰ miR-223 was predominantly expressed in naive CD4 T lymphocytes but not in Th17 cells, which were previously reported to have a role in RA. Because naive CD4 T cells from healthy donors did not consistently express miR-223 even after T-cell receptor stimulation, this suggests that miR-223 overexpression in RA is an aberration associated with pathology and not a consequence of T-lymphocyte activation in patients with RA. However, further studies are needed to clarify the exact link between this observation and RA. miR-223 might also have a critical role in the control of osteoclastogenesis, since overexpression of miR-223 suppressed the in vitro differentiation of mouse RAW264.7 macrophage cells into osteoclasts.³¹

miRNAs AS POTENTIAL BIOMARKERS IN RA

Early diagnosis and treatment are very important for preventing further disease progression in RA. In addition, some patients with RA do not respond well to methotrexate—or subsequently, to anti-TNF α treatment or B-cell depletion.³² Therefore, the use of prognostic as well as diagnostic biomarkers is highly desirable. Biomarkers could help to identify the presence of a disease before it could otherwise be easily detected. In addition, an ideal biomarker would be able to track the molecular diversity of RA and simultaneously monitor the progression of the disease. A third requisite for a biomarker is that it should reveal the response of the patient to treatment and thereby guide doctors. An overview of the biomarker field in rheumatic diseases has been written by Alevizos and Illei.³³

Current diagnostic techniques, such as joint radiography and the histological evaluation of material obtained from tissue biopsy, remain the 'gold standards' of diagnosis. Although markers greatly improve diagnosis, the invasive, unpleasant and inconvenient nature of current diagnostics remains a problem. Therefore, it would be highly desirable to identify non-invasive markers. Recently, the discovery of miRNAs in the serum of patients with cancer opened up the exciting prospect of using miRNAs as powerful, non-invasive cancer biomarkers (reviewed by Cortez and Calin³⁴). A first step toward the analysis of miRNAs as RA biomarkers was reported by Murata *et al*³⁵, who investigated whether miRNAs are also stably present in SF and whether plasma and SF miRNAs could be used as biomarkers of RA and OA. Concentrations of miR-16, miR-146a, miR-155 and miR-223 in the SF of patients with RA were significantly higher than those of OA. However, when compared with their plasma concentrations, the abundance of miR-16, miR-132, miR-146a and miR-223 was significantly lower in the SF of patients with RA and OA; thus, there was no correlation between miRNAs abundance in plasma and SF. The miRNAs in SF of RA probably originated from synovial tissues and infiltrating cells, possibly in the form of microparticles. Microparticles are small, membrane-bound vesicles that are released from activated or dying cells and are abundantly present in the SF of patients with RA and have been shown to contain miRNA.³⁶ Plasma miRNAs or the ratio of SF miRNAs to plasma miRNAs, including miR-16 and miR-146a, significantly correlated with tender joint counts and the 28-joint Disease Activity Score. In contrast, the plasma miR-132 level in healthy controls was significantly higher than that of patients with RA or OA with pronounced diagnostic power.

FUTURE PROSPECTS

Recent data suggest that miRNA deregulation could play a part in the development and sustainment of RA. The ways in which miRNAs are deregulated in RA could be manifold, from germline loss or gene amplification of miRNAs to their transcriptional deregulation, possibly by epigenetic modifications or activation (reviewed by Karouzakis *et al*³⁷). Mutations in miRNA genes could also result in the aberrant processing or expression of miRNAs, possibly also because of mutations in their promoter regions or respective host genes. Additionally, many indirect effects like mutations in the 3'-UTR of target mRNAs could be envisioned.

Table 1 Differentially regulated miRNAs in patients with RA

miRNA	Functions	mRNA targets	Reference
miR-16	► Upregulated in RA PBMCs • Synovial fluid level lower than plasma levels in patients with RA	ND	19 35
miR-124a	► Downregulated in RASFs	CDK2, MCP-1	25
miR-132	► Upregulated in RA PBMCs • Synovial fluid level lower than plasma levels in patients with RA	ND	19 35
miR-146a	► Upregulated in RA synovial tissue, RASFs and RA PBMCs • Upregulated in RA CD4 T lymphocytes from peripheral blood and synovial fluid • Synovial fluid level lower than plasma levels in patients with RA	TRAF6, IRAK1	17–19 29 35
miR-155	► Upregulated in RA synovial tissue, RASFs and RA PBMCs	MMP-3	18
miR-223	► Upregulated in RA CD4 T lymphocytes • Abundance lower in synovial fluid than in plasma of patients with RA	ND	30 35
miR-346	► Upregulated in LPS-treated RASFs	ND	22
miR-363	► Downregulated in RA CD4 T lymphocytes from peripheral blood and synovial fluid	ND	29
miR-498	► Upregulated in RA CD4 T lymphocytes from synovial fluid	ND	29

CDK2, cyclin-dependent kinase 2; IRAK1, interleukin-1 receptor-associated kinase 1; LPS, lipopolysaccharide; miRNA, microRNA; MCP-1, monocyte chemoattractant protein 1; MMP-3, matrix metalloproteinase 3; ND, not determined; PBMCs, peripheral blood mononuclear cells; RA, rheumatoid arthritis; RASFs, rheumatoid arthritis synovial fibroblasts; TRAF6, tumour necrosis factor receptor-associated factor 6.

Supplement

The candidate RA miRNAs (see table 1 for a summary) identified to date have already improved our understanding of the molecular mechanisms responsible for RA. By identifying miRNAs that target several genes that are upregulated or downregulated in patients with RA, one could manipulate several mRNAs simultaneously by overexpressing or downregulating one particular miRNA.

miRNA expression profiling in patients with RA could also be potentially useful for identifying biomarkers for assessing disease phenotype, activity, progression or response to treatment. However, larger confirmation studies for biomarkers in well-defined cohorts must first be undertaken. The use of miRNA biomarkers in RA is especially appealing, because miRNA expression and deregulation in RA joints are probably mirrored in easy-to-obtain PBMCs or T cells.

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