The Role of Micro-RNAs in Rheumatic Diseases: An Update

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1. Introduction

MicroRNAs (miRNAs) are small non-coding RNAs of approximately 22 nucleotides in length, whose main function is to modulate the expression of multiple target genes at the post-transcriptional level through messenger-RNA (mRNA) degradation or repression of translation [1-3]. More than 30% of all human genes are regulated by miRNAs, with each miRNA controlling multiple mRNA targets, and each mRNA targeted by various miRNAs [2]. These intriguing molecules have been first described in 1993 in *Caenorhabditis elegans* [4] and first demonstrated in humans in 2001 [5]. Since then, several miRNAs have been identified and more than 2,042 miRNAs have been described in humans to date (miRBase release 19, at [http:// www.mirbase.org/](http://www.mirbase.org/)).

MiRNA play a crucial role in modulating a large range of biologic functions from developmental timing to organogenesis [6,7]. They have a key role in cellular differentiation, homeostasis, apoptosis and anti-viral defence [1,8]. More recently, it has become evident that miRNAs play a crucial role in the development of immune cells and in regulating the immune response [9-11].

Altered expression of miRNAs profiles has been initially related to the development of cancer and subsequently to various non-malignant diseases such as cardiovascular disorders, lung diseases, schizophrenia, Alzheimer disease, neuro psychiatric disorders, viral infections, primary biliary cirrhosis and chronic inflammatory and autoimmune diseases [12-17]

In the last two decades, increasing evidences have linked miRNA abnormal expression with pathogenic mechanisms of cancer, and a lot of causes that led to their dysregulation have been discovered [18]. Many miRNAs have been associated with cancer development [19,20],

metastatic capability [21] and resistance to anti-cancer drugs [22]. In this field, they are also considered as new potential diagnostic and prognostic biomarkers [20, 23]. Furthermore the application of miRNAs as a candidate molecular target for anticancer therapeutics seems very promising [18,24].

More recently, some studies have highlighted the role of miRNAs in the development of several rheumatic diseases [25-33] and this argument today represents an emerging and exciting field of research. This is not surprising since miRNAs altered expression may lead either to persistent inflammation or to impaired tolerance against self-antigens, thus promoting the development of both autoimmune and inflammatory chronic diseases [11, 34].

In this article we summarize the new acquisitions about the growing importance of miRNAs in rheumatic diseases as pathogenetic factors, potential biomarkers and possible new therapeutic targets. We also focus on new developments about the possible role of miRNA in the pathogenesis of psoriatic arthritis (PsA) on the basis of our recent experimental results.

2. MiRNAs in rheumatic diseases

2.1. Connective tissue disorders

2.1.1. Systemic lupus erythematosus

Systemic lupus erythematosus (SLE) is an autoimmune systemic disease of unknown etiology characterized by abnormal autoantibody production, inflammatory involvement of various organ systems including skin, mucous membranes, joints, serous membranes, kidney, brain, lung and heart and significant morbidity and mortality [35]. A number of studies carried out so far, have demonstrated that miRNA have an important role in SLE pathogenesis and can be predictive of disease activity and severity, helpful as biomarkers and useful for development of new therapeutic strategies [36-42].

In the study of Dai et al. [36], peripheral blood mononuclear cell (PBMC) miRNA profiles of 23 patients with SLE, 10 healthy controls and 10 patients with idiopathic thrombocytopenic purpura (ITP) were analyzed. In comparison with healthy controls, miRNA microarray analysis identified 19 miRNA differentially expressed in ITP (14 down-regulated and 5 up-regulated) and 16 miRNAs differentially expressed in SLE (7 down-regulated: miR-196a, miR-17-5p, miR-409-3p, HMP-PREDICTED-miR141, miR-383, HMP-PREDICTED-miR112 and miR-184; and 9 up-regulated: HMP-PREDICTED-miR189, HMP-PREDICTED-miR-61, HMP-PREDICTED-miR78, miR-21, miR-142-3p, miR-342, miR-299-3p, miR-198 and mmu-miR-298). Interestingly, from the comparison between the two pathologic groups, 13 miRNAs resulted dysregulated both in SLE and ITP, 6 downregulated in ITP only, and finally 3 dysregulated in SLE only: miR-184 (underexpressed) and miR198 and miR21 (overexpressed) [36]. Furthermore, 8 miRNA (miR-494, miR-188, miR-501, mmu-miR-298, HMP-PREDICTED-miR61, HMP-PREDICTED-miR78, miR-296 and miR-299-3p) were downregulated in SLE patients with more active disease (SLE Disease Activity Index score

[SLEDAI] ≥ 15) in comparison with patients with inactive disease (SLEDAI ≤ 12), which led to hypothesized that these 8 miRNA could be involved in SLE progress, recrudescence and organ injure [36]. The same group examined miRNA expression in renal biopsy of patients with WHO Class II lupus nephritis (LN), showing 66 dysregulated miRNA (36 up- and 30 down-regulated) in comparison with healthy controls [37].

Te et al. investigated PBMCs miRNA expression profile of LN patients (African American and European American) in comparison with unaffected controls and found 5 miRNA differentially expressed in LN: 4 up-regulated (miR-371-5P, miR-423-5P, miR-638 and miR-663) and 1 down-regulated (miR-1224-3P) [43]. In particular, miR-371-5P, miR-423-5P and miR-1224-3P were reported for the first time to be associated with lupus nephritis [43].

In a study performed by using the TaqMan miRNA assay, Tang et al. showed in SLE PBMCs 42 miRNAs differentially expressed in comparison with healthy controls, with 7 miRNA being more than six-fold down-regulated in SLE: miR-31, miR-95, miR-99a, miR-130b, miR-10a, miR-134, and miR-146a [40]. Notably, underexpression of miR-146a negatively correlated with clinical disease activity and with interferon (IFN) scores in SLE patients. Moreover, inhibition of endogenous miR-146a in PBMCs through transfection with synthetic miRNA-146a hairpin inhibitor increased the induction of type I IFN, which is known to have a role in the pathogenesis of SLE. These findings highlighted that underexpression of miR-146a could have an important role in the pathogenesis of SLE, thus providing potential novel strategies for therapeutic intervention [40].

Consistent with these results, Wang et al. showed that in SLE patients serum miR-146a and miR-155 levels were lower, and the urinary level of miR-146a was higher in comparison with healthy controls [44]. Moreover, estimated glomerular filtration rate (eGFR) correlated with both serum miR-146a and miR-155, and serum miR-146a inversely correlated with proteinuria and the SLE Disease Activity Index, which suggested that both miR-146a and miR-155 participated in the pathophysiology of SLE and might be used as biomarkers of SLE [44]. The same authors recently confirmed that urinary levels of miR-146a and miR-155 in patients with SLE were significantly higher than that in healthy controls [45]. In another study they also evidenced that the serum levels of miR-200a, miR-200b, miR-200c, miR-429, miR-205 and miR-192, and urinary levels of miR-200a, miR-200c, miR-141, miR-429 and miR-192 of SLE patients were lower than those of controls, with SLEDAI index that inversely correlated with serum miR-200a [46]. Hai-yan et al. confirmed in their study the lower expression of miR-146a in PBMCs of SLE patients compared to healthy controls [47].

In comparison with healthy controls, miR-21 and miR-148a [48] and miR-126 [42] resulted up-regulated in SLE CD4⁺ T cells and promoted cell hypomethylation by repressing DNA methyltransferase 1 (DNMT1) expression, which led to hypothesized that they contribute to T cell autoreactivity in SLE.

Compared with controls, miR-21 has been also found upregulated in SLE CD4⁺ T lymphocytes by Stagakis et al. [39]. MiR21 strongly correlated with SLE disease activity and investigation of putative gene-targets showed that it suppressed PDCD4, thus regulating aberrant T cell responses in human SLE.

Most recently, Ding et al. demonstrated that miR-142-3p/5p were significantly down-regulated in SLE CD4+ T cells compared with healthy controls and that their reduced expression caused T cell activity and B cell hyperstimulation[49]. Lu et al. showed a different intra-renal expression of miR-638, miR-198 and miR-146a between LN patients and normal controls [38]. In particular, miR-638 had lower glomerular expression and higher tubulointerstitial expression; miR-198 resulted up-regulated in both glomerulus and in tubulointerstitium; and miR-146a was overexpressed in glomerulus. Interestingly, tubulointerstitial miR-638 expression significantly correlated with clinical disease severity (estimated GFR/histological activity index and proteinuria/disease activity score, respectively), while glomerular miR-146a expressions were correlated with estimated GFR and histological activity index [38].

Main miRNA dysregulated in SLE are shown in Tab.1.

Up-regulated	Down-regulated
-miR198 and miR21 (PBMC)[36]	-miR-184 (PBMC) [36]
-miR-371-5P,miR-423-5P, miR-638 and miR-663 (PBMC)[43]	-miR-1224-3P (PBMC) [43]
-miR-21 and miR-148a (CD4+ T cells)[48]	- miR-31, miR-95, miR-99a, miR-130b, miR-10a, miR-134, and miR-146a (PBMC) [40]
-miR-21 (CD4+ T cells) [39]	-miR-146a and miR-155 (serum) [44]
-miR-126(CD4+ T cells)[42]	-miR-142-3p/5p (CD4+ T cells) [49]
-miR-638, miR-198 and miR-146a (intra-renal) [38]	-miR-638 (intra-renal) [38]
	-miR-146a (urine)[44]

Abbreviations: PBMC, peripheral blood mononuclear cells

Table 1. Main microRNA dysregulated in SLE

2.1.2. Sjögren Syndrome (SS)

SS is an inflammatory autoimmune disease primarily affecting the exocrine glands and characterized by the presence of typical autoantibodies such as anti-Ro (SSA) and anti-La (SSB), keratoconjunctivitis sicca, xerostomia, pulmonary involvement, nonerosive polyarthritits and increased risk of lymphoid malignancy [50]. The relatively easy access to the target tissue (salivary glands and saliva) makes Sjogren's syndrome appealing to study microRNAs [41]. Michael et al. demonstrated a prominent difference between miRNAs profile in saliva obtained from patients with SS and healthy donors [51]. Alevizos et al. showed a different miRNA expression profile in glands of SS in comparison with controls. Moreover, in half of the patients with a focus score of 12, the miR-17-92 cluster resulted downregulated [52].

Lu et al. showed that miR-574 and miR-768-3p resulted overexpressed in the SS salivary glands, while miRNA-146a was increased in PBMCs and salivary glands [53]. Interestingly, the overexpression of miR146a was confirmed in PBMC of patients with SS [54, 55] as well as in PBMCs and in the salivary glands of a SS mouse model [54]. These results are promising for the development of future diagnostic and prognostic biomarkers in SS.

Main miRNA dysregulated in SS are shown in Tab.2.

Up-regulated	Down-regulated
-miR-574 and miR-768-3p (salivary glands) [53]	miR-17-92 (salivary glands) [52]
-miR-146a (PBMCs and salivary glands) [53]	
-miR-146a (PBMCs) [54, 55]	

Abbreviations: PBMC, peripheral blood mononuclear cells

Table 2. Main microRNA dysregulated in SS

2.1.3. Systemic Sclerosis (SSc)

SSc is a generalized connective tissue disease affecting skin and internal organs and characterized by abnormal extracellular collagen accumulation. It is typically associated with specific autoantibodies (anticentromere and anti-topoisomerase Scl-70) [56].

Recently, Maurer et al. found that miR-29a was strongly down-regulated in SSc fibroblasts and skin sections as compared with the healthy controls and, similarly to human SSc, the expression of miR-29a was reduced in the bleomycin model of skin fibrosis [57]. Interestingly, overexpression in SSc fibroblasts decreased, and knockdown in normal fibroblasts increased the levels of messenger RNA for type I and type III collagen, which highlighted the role of miR-29a as post-transcriptional regulators of pro-fibrotic genes [57]. These results appear very intriguing and reveal that miR29 could be considered a potential therapeutic target in SSc [57, 58]. In comparison with the normal skin tissues, Zhu et al. identified some miRNAs aberrantly expressed in limited cutaneous scleroderma and diffuse cutaneous scleroderma skin tissues, such as miR-21 (up-regulated) and miR-145 and miR-29b (down-regulated) both in the skin tissues and fibroblasts [59].

Main miRNA dysregulated in SSc are shown in Tab.3.

Up-regulated	Down-regulated
-miR-21 (SSc skin tissues and fibroblasts)[59]	-miR-29a (SSc fibroblasts) [57]
	-miR-145 and miR-29b (SSc skin tissues and fibroblasts) [59]

Table 3. Main microRNA dysregulated in SSc

2.2. Osteoarthritis (OA)

OA is the most common age related disorder whose main features are the damage of the articular cartilage, the increased activity in the subchondral bone and osteophyte formation. A moderate synovitis may appear especially in advanced cases [60]. In comparison with normal cartilage, Iliopoulos et al. evidenced 16 miRNAs differentially expressed in OA cartilage [61].

Out of these, miR-22 resulted up-regulated and contributed to decreased expression of aggrecan and increased levels of IL-1b and MMP-13 in chondrocytes, while miR-140 was found down-regulated and its under-expression was related to the development of age-related OA-like changes [61]. In the cartilage of late-stage OA, Jones et al. described several differentially expressed miRNAs, out of these miR-146a resulted down-regulated, miR-9 and miR-98 up-regulated [62]. Interestingly, functional analysis revealed that miR-9 and miR-98 reduced the IL-1 β -induced production of TNF α in primary chondrocytes, while miR-9 also inhibited MMP-13 secretion in vitro, a scenario which led to hypothesized their protective role in OA [62]. MiR-27a was also found down-regulated in OA chondrocytes and its underexpression indirectly inhibited MMP-13 and IGFBP-5 (insulin-like growth factor binding protein) [63]. A protective role on OA cartilage and in modulating pain symptoms has been hypothesized for miR-146A [64]. Most recently, overexpression of miR-146a, miR-155, miR-181a and miR-223 was demonstrated in PBMCs of OA patients in comparison with healthy controls, with miR-146a and miR-223 significantly higher in the early stages of OA than at later stages [65].

However, although several OA-associated miRNA have been reported to date, their potential role in OA needs to be further elucidated and their targets need to be discovered in the future.

Main miRNA dysregulated in OA are shown in Tab.4

Up-regulated	Down-regulated
-miR-22 (OA cartilage) [61]	-miR-140 (OA cartilage) [61]
-miR-9 and MiR-98 (OA cartilage) [62]	-miR-146a (OA cartilage) [62]
-miR-146a, miR-155, miR-181a (OA PBMCs) [65]	-miR-27a (OA chondrocytes) [63]

Abbreviations: PBMC, peripheral blood mononuclear cells

Table 4. Main microRNA dysregulated in OA

2.3. Rheumatoid arthritis

Rheumatoid arthritis (RA) is a chronic inflammatory joint disorder that is characterized by immune-driven inflammation of synovial membrane which results in erosion, joint destruction and disability. Extra-articular symptoms, such as serositis, nodules and vasculitis are common and usually associated to a more severe disease. The etiology of rheumatoid arthritis (RA) is still unknown, and many uncertainties regarding its pathogenetic mechanisms persist yet [66].

Many recent studies have demonstrated that different miRNAs are significantly dysregulated in RA tissues.

2.3.1. Synovium

In comparison with healthy controls and/or OA patients, some miRNA have been found up-(miR-155, miR-203 and miR-146a) or down-(miR124a and miR-34a*) regulated in RA synovial tissue and/or synovial fluid [67-74].

MiR-155 has emerged as one of the most attractive and thoroughly studied miRNA in RA. It was found significantly up-regulated in RA-synovial fibroblasts (RA-SFs) [74], in the lining layer CD68+ macrophages [68] and in synovial fluid CD14+ cells [68, 74] of the RA synovial compartment.

Since overexpression of miR-155 in RA-SFs was shown to decrease the levels of matrix metalloproteinase 3 (MMP-3) and 1 (MMP-1) *in vitro*, it was initially hypothesized a protective role of miR-155 by modulating destructive properties of RA-synovial fibroblasts (RA-SFs) [74]. However, *in vivo* data have shown an opposite role for miR-155 in the development of arthritis [68, 75]. Up-regulation of miR-155 in synovial fluid CD14+ cells increased the expression of TNF- α , IL-1 β , IL-6, and IL-8 and downregulated the expression of the miR-155 target SHIP-1 (Src homology 2-containing inositol phosphatase-1), an inhibitor of inflammation [68], and miR-155-deficient mice are resistant to collagen-induced arthritis [75]. These data, together with the observation that specific inhibition of miR-155 in RA synovial macrophages reduced TNF-alpha production led to ascribe to miR-155 a role in excessive proinflammatory activation of myeloid cells in RA and to suggest that miR-155 may represent an intriguing therapeutic target [68]. Interestingly, Worm et al. first reported on miR-155 silencing *in vivo* in a mouse inflammation model [76], which further underlines the potentiality of miR-155 antagonists as novel therapeutics for treatment of chronic inflammatory diseases.

MiR-203, was found significantly up-regulated in RA-SFs in comparison with OA-SFs [73]. It resulted in higher release of MMP-1 and secretion of IL-6 via the NF-kappa B pathway, which led to hypothesize a role in activating RA-SFs and triggering inflammation [73]. However, the direct targets of miR-203 in RA-SFs still need to be highlighted [73].

Mir-146a resulted greatly expressed in RA synovial tissue when compared with OA and it has been demonstrated in CD3+ T cells, IL-17 producing T cells, CD68+ cells, in some B lymphocytes [70, 72, 74] and in RA-SF, where its expression resulted induced by several pro-inflammatory mediators such as TNF-alpha and IL-1beta [70, 74]. However, its role in synovial tissue has yet to be elucidate.

MiR-124a was found significantly lower in RA-SFs in comparison with OA [69]. Its down-regulation appears to play an important role in the pathogenesis of RA by mediating the enhancement of both cyclin-dependent kinase 2 (CDK-2), involved in the cell cycle regulation, and monocyte chemoattractant protein 1 (MCP-1), which are able to attract into the synovial tissue inflammatory cells, memory T lymphocytes and natural killer cells [67, 69]. These intriguing findings have suggested that miR-124a could also have a therapeutic potential [67, 69].

Finally miR-34a* was found significantly down-regulated in RA-SFs in comparison with OA as a result of higher DNA methylation, which would contribute to the RA-SFs resistance to apoptosis, a typical feature of these RA cells [71]

2.3.2. Blood

MiR-146a was found overexpressed in PBMC obtained from RA patients, especially those with early RA and with high disease activity, compared with healthy and disease control individuals [72, 77]. Other studies confirmed miR-146a overexpression in PBMC [78], in CD4+

T lymphocytes from peripheral blood [79] and in plasma [80] of RA patients. The observation that miR-146a was able to silence in PBMC the expression of interleukin-1 receptor-associated kinase 1 (IRAK1) and TNF receptor associated factor 6 (TRAF6), members of the TLR4 signaling cascade [81], led to hypothesized that miR-146a could act as a negative regulator of inflammation, as supported by other recent studies [77, 82, 83]. However, in the study of Pauley et al. PBMC expression of IRAK-1 and TRAF6 was no different between RA patients and healthy controls, as expected [77], which led to hypothesized that was a defect in regulation of these molecules by miR-146a that promoted inflammation, with an extensive and prolonged TNF-alpha production [77].

Consistent with the data on synovial compartment, miR-155 has been found increased in PBMC from RA patients compared with healthy controls and upregulated during the differentiation of IL-17 producing cells [72, 77]. Conversely, concentrations of miR-155 and other examined miRNA (miR-16, miR-132, miR-146a and miR-223) resulted not differently expressed between RA and OA patients in plasma, although plasma levels of miR-155,miR-16, miR-146a and miR-223 inversely correlated with clinical indices, such as tender joint count and 28-joint Disease Activity Score (DAS 28).

Recently, Fulci et al showed a clear up-regulation of miR-223 and a significant downregulation of miR-142, miR-28 and miR-30e in T-lymphocytes from peripheral blood from RA patients in comparison with healthy controls [84]. The same group confirmed the overexpression of miR-223 in T-lymphocytes of early rheumatoid arthritis patients [85] which led the authors to speculate that this aberrant over-expression could contribute to the pathogenesis of the disease.

Other miRNAs resulted dysregulated in RA, such as miR-16, miR-132, miR-26a, and miR-150 which resulted up-regulated in PBMC from patients with RA compared with healthy controls. [72, 77]. Of these, miR-16 and miR-150 correlated with disease activity [72, 77], whereas miR-26 and miR-150 resulted upregulated in IL-17 producing T cells [72].

Main miRNA dysregulated in RA are shown in Tab.5

Up-regulated	Down-regulated
-miR-155 (synovium) [68, 74]	-miR-124a (synovium) [69]
-miR-155 (PBMC) [72, 77]	-miR-34a* (synovium) [71]
-miR-203 (synovium) [73]	
-miR-146a (synovium) [70, 72, 74]	
-miR-146a (PBMC/ CD4+ T lymphocytes/plasma) [72, 77-80]	
-miR-223 (blood T-lymphocytes [84, 85]	
- miR-16, miR-132, miR-26a, and miR-150 (PBMC) [72, 77]	

Abbreviations: PBMC, peripheral blood mononuclear cells

Table 5. Main microRNA dysregulated in RA

2.4. Psoriatic arthritis

Psoriatic arthritis (PsA) is a chronic inflammatory disease that develops in ~ 20% of individuals with psoriasis [86]. PSA pathogenesis is not yet fully understood and lymphocytes, in particular CD8+ T cells, appear to play an important role in the pathogenesis of both psoriasis and PsA [87, 88]. In addition, several pro-inflammatory cytokines seem to be involved, including TNF- α , IL-1, IL-6 and IL-12 [89-91]. While several studies have shown an altered expression of miRNAs in psoriasis, to date – at the best of our knowledge - no studies have been performed about the miRNA expression profile in PsA. On this background, we evaluated a comprehensive global miRNA expression profile in PBMCs of patients with PsA in comparison with healthy controls, with the main purpose to characterise the miRNA signature in PsA (*Clin Drug Investig, in press*). Below, the results of the principal studies on psoriasis and the main results of our study on PsA are summarized.

2.4.1. Psoriasis

Several miRNA have been found dysregulated in psoriatic skin when compared with healthy skin, such as miR-203, miR-146a, miR-99a and miR-21 (up-regulated) or miR 125b (down-regulated).

Up-regulation of miR-203 correlated with the underexpression of SOCS-3 (suppressor of cytokine signalling 3) which is implicated in inflammatory response and keratinocyte functions [92]. Recently, Primo et al. confirmed the up-regulation of miR-203 in psoriatic lesions, with TNF- α and IL24 as its direct targets [93]. The over-expressed miR-146a was related to the TNF- α signalling control in the skin [94]. Up-regulation of miR-99a was correlated with a slow keratinocyte proliferation and induction of their differentiation through regulation of IGF-1R [95]. Elevated levels of miR-21 in psoriatic skin have been found by Meisgen et al. [96]. The authors evidenced that overexpression of this miRNA was related to apoptosis suppression in activated T cells, which contributed to T cell-derived psoriatic skin inflammation [96].

Downregulation of miR-125b has been associated with high TNF- α production [94] and with the modulation of keratinocyte differentiation and proliferation by targeting FGFR2 (fibroblast growth factor receptor 2) [97].

Other miRNA have been found dysregulated in psoriasis. Zibbert et al. identified 42 upregulated miRNAs and 5 downregulated miRNAs in psoriasis skin compared with healthy skin [98]. Out of these, up-regulated miR-21, miR-205, miR-221 and miR-222 were found to have potential mRNA targets in psoriatic skin such as PDCD4, TPM1, P57, C-KIT, RTN4, SHIP2, TIMP3, RECK and NFIB, which were likely to be involved in cellular growth, proliferation, apoptosis and degradation of the extracellular matrix [98].

Down-regulation of miR-424 in the skin [99] and up-regulation of miR-1266 in the serum [100] of PsA patients have also been demonstrated. Underexpression of miR-124 was related to increased levels of MEK1 or cyclin E1 proteins, thus to enhanced keratinocyte proliferation [99]. Overexpression of miR-1266 in the PsA serum was quite unexpected being this miRNA a putative regulator of IL-17A, a key cytokine in PsA pathogenesis, so

the authors hypothesized that miR-1266 could be involved in the pathogenesis of psoriasis by regulating other target molecules [100].

Main miRNA dysregulated in psoriasis are shown in Tab.6.

Up-regulated	Down-regulated
-miR-203 (psoriatic skin) [92, 93]	-miR 125b (psoriatic skin) [92]
-miR-146a (psoriatic skin) [92]	-miR-424 (psoriatic skin) [99]
-miR-99a (psoriatic skin) [95]	
-miR-21 (psoriatic skin) [96]	
-miR-21, miR-205, miR-221 and miR-222 (psoriatic skin)[98]	
-miR-1266 (serum) [100]	

Table 6. Main microRNA dysregulated in Psoriasis

2.4.2. Psoriatic arthritis

In our recent study (*Clin Drug Investig, in press*), we evaluated global miRNA expression profile in PBMCs of 13 patients with early active and untreated PsA. In comparison with healthy controls, the PBMC of PsA group revealed the presence of 9 up-modulated and 7 down-regulated miRNAs. Within the group of up-regulated, miR-21, miR-34a and miR-125a appeared of particular interest considering the extent of their modulation and their emerging role in inflammatory processes (*Clin Drug Investig, in press*) (Tab.7). Instead, all down-regulated miRNAs belonged to two large adjacent miRNA clusters located on chromosome 14, which makes this chromosome worthy of further investigation in the field of psoriasis and PsA genetic susceptibility (*Clin Drug investig, in press*). Quantitative RT-PCR (RT-qPCR) analysis for specific miRNA (miR-21, miR-34a, miR-125a), performed in the entire series of 13 PsA patients plus 5 additional PsA patients and in healthy controls, confirmed the up-regulation of these three miRNA (unpublished data). (Figure 1A-C). Moreover, based on its emerging role in immunity control and the proved involvement in other autoimmune diseases [40, 77, 81, 101, 102] we also evaluated by RT-qPCR miR-146a levels in the entire group of 18 PsA patients. Also in this case, real time results were in agreement with microarray and did not show significant differences between patients and controls (unpublished data) (Figure 1D). The demonstration of a miRNA signature in PsA could be a novel starting point for understanding pathogenic mechanisms of this disease. Moreover, altered miRNAs expression in patients with active disease makes them attractive as potential biomarkers of disease.

Up-regulated	Down-regulated
MiR-21, miR-34a and miR-125a (PBMC) (Ciancio et al., Clin Drug Investig,in press)	
Abbreviations: PBMC, peripheral blood mononuclear cells	

Table 7. Main microRNA dysregulated in PsA

Figure 1. Validation of miR-34a (A), miR-21 (B), miR-125a (C) and miR-146a (D) levels by quantitative RT-PCR. MiRNAs expression in 18 PsA patients and 8 controls was quantified using RT-qPCR. Each expression data was normalized on endogenous U6 RNA level by 2- Δ Ct method. Each sample was analyzed in triplicate. Data are displayed using vertical scatter plot (GraphPad v.5), bars represent means $\pm$ SEM. Two-tailed t-test was used to determine the p-values.

3. Conclusions

MiRNA are fine regulators of gene expression at the post-transcriptional level and it is today known that they participate in the regulation of almost every aspect of cell physiology, including the development of immune cells and the regulation of the immune response.

MiRNA altered expression has been related to the development of several chronic inflammatory and autoimmune diseases such as systemic lupus erythematosus, rheumatoid arthritis, Sjogren syndrome, systemic sclerosis, psoriasis and psoriatic arthritis. Osteoarthritis, the most common age related disorder, seems also to be related to an altered expression of miRNAs. Besides their crucial role in the pathogenesis of rheumatic diseases, miRNAs can also be predictive of disease activity and severity, helpful as biomarkers and useful for development of new therapeutic strategies. However, this exciting field of research is still at an early stage and larger studies are still desirable to define the specific roles that individual miRNAs may play in rheumatic diseases.

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References

- [1] Ambros V. The functions of animal microRNAs. *Nature* 2004;431(7006):350-5.
- [2] Guo H, Ingolia NT, Weissman JS, Bartel DP. Mammalian microRNAs predominantly act to decrease target mRNA levels. *Nature* 2010;466(7308):835-40.
- [3] Lagos-Quintana M, Rauhut R, Lendeckel W, Tuschl T. Identification of novel genes coding for small expressed RNAs. *Science* 2001;294(5543):853-8.
- [4] Lee RC, Feinbaum RL, Ambros V. The *C. elegans* heterochronic gene *lin-4* encodes small RNAs with antisense complementarity to *lin-14*. *Cell* 1993;75(5):843-54.
- [5] Hutvagner G, McLachlan J, Pasquinelli AE, Balint E, Tuschl T, Zamore PD. A cellular function for the RNA-interference enzyme Dicer in the maturation of the *let-7* small temporal RNA. *Science* 2001;293(5531):834-8.
- [6] Ambros V. MicroRNA pathways in flies and worms: growth, death, fat, stress, and timing. *Cell* 2003;113(6):673-6.
- [7] Bartel DP. MicroRNAs: genomics, biogenesis, mechanism, and function. *Cell* 2004;116(2):281-97.
- [8] Krek A, Grun D, Poy MN, et al. Combinatorial microRNA target predictions. *Nat Genet* 2005;37(5):495-500.
- [9] Baltimore D, Boldin MP, O'Connell RM, Rao DS, Taganov KD. MicroRNAs: new regulators of immune cell development and function. *Nat Immunol* 2008;9(8):839-45.
- [10] Lodish HF, Zhou B, Liu G, Chen CZ. Micromanagement of the immune system by microRNAs. *Nat Rev Immunol* 2008;8(2):120-30.
- [11] Lu LF, Liston A. MicroRNA in the immune system, microRNA as an immune system. *Immunology* 2009;127(3):291-8.

- [12] Houzet L, Yeung ML, de Lame V, Desai D, Smith SM, Jeang KT. MicroRNA profile changes in human immunodeficiency virus type 1 (HIV-1) seropositive individuals. *Retrovirology* 2008;5:118.
- [13] Jiang Q, Wang Y, Hao Y, et al. miR2Disease: a manually curated database for microRNA deregulation in human disease. *Nucleic Acids Res* 2009;37(Database issue):D98-104.
- [14] Niwa R, Zhou F, Li C, Slack FJ. The expression of the Alzheimer's amyloid precursor protein-like gene is regulated by developmental timing microRNAs and their targets in *Caenorhabditis elegans*. *Dev Biol* 2008;315(2):418-25.
- [15] Padgett KA, Lan RY, Leung PC, et al. Primary biliary cirrhosis is associated with altered hepatic microRNA expression. *J Autoimmun* 2009;32(3-4):246-53.
- [16] Sarasin-Filipowicz M, Krol J, Markiewicz I, Heim MH, Filipowicz W. Decreased levels of microRNA miR-122 in individuals with hepatitis C responding poorly to interferon therapy. *Nat Med* 2009;15(1):31-3.
- [17] Zhu Y, Kalbfleisch T, Brennan MD, Li Y. A MicroRNA gene is hosted in an intron of a schizophrenia-susceptibility gene. *Schizophr Res* 2009;109(1-3):86-9.
- [18] Schoof CR, Botelho EL, Izzotti A, Vasquez Ldos R. MicroRNAs in cancer treatment and prognosis. *Am J Cancer Res* 2012;2(4):414-33.
- [19] Galasso M, Sandhu SK, Volinia S. MicroRNA expression signatures in solid malignancies. *Cancer J* 2012;18(3):238-43.
- [20] Lu J, Getz G, Miska EA, et al. MicroRNA expression profiles classify human cancers. *Nature* 2005;435(7043):834-8.
- [21] Lopez-Camarillo C, Marchat LA, Arechaga-Ocampo E, et al. MetastamiRs: Non-Coding MicroRNAs Driving Cancer Invasion and Metastasis. *Int J Mol Sci* 2012;13(2):1347-79.
- [22] Rodrigues AS, Dinis J, Gromicho M, Martins C, Laires A, Rueff J. Genomics and cancer drug resistance. *Curr Pharm Biotechnol* 2012;13(5):651-73.
- [23] Calin GA, Ferracin M, Cimmino A, et al. A MicroRNA signature associated with prognosis and progression in chronic lymphocytic leukemia. *N Engl J Med* 2005;353(17):1793-801.
- [24] Rutnam ZJ, Yang BB. The involvement of microRNAs in malignant transformation. *Histol Histopathol* 2012;27(10):1263-70.
- [25] Baxter D, McInnes IB, Kurowska-Stolarska M. Novel regulatory mechanisms in inflammatory arthritis: a role for microRNA. *Immunol Cell Biol* 2012;90(3):288-92.
- [26] Ceribelli A, Nahid MA, Satoh M, Chan EK. MicroRNAs in rheumatoid arthritis. *FEBS Lett* 2011;585(23):3667-74.

- [27] Ceribelli A, Yao B, Dominguez-Gutierrez PR, Nahid MA, Satoh M, Chan EK. MicroRNAs in systemic rheumatic diseases. *Arthritis Res Ther* 2011;13(4):229.
- [28] Duroux-Richard I, Jorgensen C, Apparailly F. What do microRNAs mean for rheumatoid arthritis? *Arthritis Rheum* 2012;64(1):11-20.
- [29] Duroux-Richard I, Presumey J, Courties G, et al. MicroRNAs as new player in rheumatoid arthritis. *Joint Bone Spine* 2011;78(1):17-22.
- [30] Furer V, Greenberg JD, Attur M, Abramson SB, Pillinger MH. The role of microRNA in rheumatoid arthritis and other autoimmune diseases. *Clin Immunol* 2010;136(1):1-15.
- [31] Nakasa T, Nagata Y, Yamasaki K, Ochi M. A mini-review: microRNA in arthritis. *Physiol Genomics* 2011;43(10):566-70.
- [32] Tili E, Michaille JJ, Costinean S, Croce CM. MicroRNAs, the immune system and rheumatic disease. *Nat Clin Pract Rheumatol* 2008;4(10):534-41.
- [33] Wittmann J, Jack HM. microRNAs in rheumatoid arthritis: midget RNAs with a giant impact. *Ann Rheum Dis* 2011;70 Suppl 1:i92-6.
- [34] Sonkoly E, Pivarcsi A. Advances in microRNAs: implications for immunity and inflammatory diseases. *J Cell Mol Med* 2009;13(1):24-38.
- [35] Boumpas DT, Austin HA, 3rd, Fessler BJ, Balow JE, Klippel JH, Lockshin MD. Systemic lupus erythematosus: emerging concepts. Part 1: Renal, neuropsychiatric, cardiovascular, pulmonary, and hematologic disease. *Ann Intern Med* 1995;122(12):940-50.
- [36] Dai Y, Huang YS, Tang M, et al. Microarray analysis of microRNA expression in peripheral blood cells of systemic lupus erythematosus patients. *Lupus* 2007;16(12):939-46.
- [37] Dai Y, Sui W, Lan H, Yan Q, Huang H, Huang Y. Comprehensive analysis of microRNA expression patterns in renal biopsies of lupus nephritis patients. *Rheumatol Int* 2009;29(7):749-54.
- [38] Lu J, Kwan BC, Lai FM, et al. Glomerular and tubulointerstitial miR-638, miR-198 and miR-146a expression in lupus nephritis. *Nephrology (Carlton)* 2012;17(4):346-51.
- [39] Stagakis E, Bertsias G, Verginis P, et al. Identification of novel microRNA signatures linked to human lupus disease activity and pathogenesis: miR-21 regulates aberrant T cell responses through regulation of PDCD4 expression. *Ann Rheum Dis* 2011;70(8):1496-506.
- [40] Tang Y, Luo X, Cui H, et al. MicroRNA-146A contributes to abnormal activation of the type I interferon pathway in human lupus by targeting the key signaling proteins. *Arthritis Rheum* 2009;60(4):1065-75.

- [41] Alevizos I, Illei GG. MicroRNAs as biomarkers in rheumatic diseases. *Nat Rev Rheumatol* 2010;6(7):391-8.
- [42] Zhao S, Wang Y, Liang Y, et al. MicroRNA-126 regulates DNA methylation in CD4+ T cells and contributes to systemic lupus erythematosus by targeting DNA methyltransferase 1. *Arthritis Rheum* 2011;63(5):1376-86.
- [43] Te JL, Dozmorov IM, Guthridge JM, et al. Identification of unique microRNA signature associated with lupus nephritis. *PLoS One* 2010;5(5):e10344.
- [44] Wang G, Tam LS, Li EK, et al. Serum and urinary cell-free MiR-146a and MiR-155 in patients with systemic lupus erythematosus. *J Rheumatol* 2010;37(12):2516-22.
- [45] Wang G, Tam LS, Kwan BC, et al. Expression of miR-146a and miR-155 in the urinary sediment of systemic lupus erythematosus. *Clin Rheumatol* 2012;31(3):435-40.
- [46] Wang G, Tam LS, Li EK, et al. Serum and urinary free microRNA level in patients with systemic lupus erythematosus. *Lupus* 2011;20(5):493-500.
- [47] Hai-yan W, Yang L, Mei-hong C, Hui Z. Expression of MicroRNA-146a in peripheral blood mononuclear cells in patients with systemic lupus Erythematosus. *Zhongguo Yi Xue Ke Xue Yuan Xue Bao* 2011;33(2):185-8.
- [48] Pan W, Zhu S, Yuan M, et al. MicroRNA-21 and microRNA-148a contribute to DNA hypomethylation in lupus CD4+ T cells by directly and indirectly targeting DNA methyltransferase 1. *J Immunol* 2010;184(12):6773-81.
- [49] Ding S, Liang Y, Zhao M, et al. Decreased microRNA-142-3p/5p expression causes CD4+ T cell activation and B cell hyperstimulation in systemic lupus erythematosus. *Arthritis Rheum* 2012;64(9):2953-63.
- [50] Moutsopoulos HM. Sjogren's syndrome: autoimmune epithelitis. *Clin Immunol Immunopathol* 1994;72(2):162-5.
- [51] Michael A, Bajracharya SD, Yuen PS, et al. Exosomes from human saliva as a source of microRNA biomarkers. *Oral Dis* 2010;16(1):34-8.
- [52] Alevizos I, Illei GG. MicroRNAs in Sjogren's syndrome as a prototypic autoimmune disease. *Autoimmun Rev* 2010;9(9):618-21.
- [53] Lu Q, Renaudineau Y, Cha S, et al. Epigenetics in autoimmune disorders: highlights of the 10th Sjogren's syndrome symposium. *Autoimmun Rev* 2010;9(9):627-30.
- [54] Pauley KM, Stewart CM, Gauna AE, et al. Altered miR-146a expression in Sjogren's syndrome and its functional role in innate immunity. *Eur J Immunol* 2011;41(7):2029-39.
- [55] Zilahi E, Tarr T, Papp G, Griger Z, Sipka S, Zeher M. Increased microRNA-146a/b, TRAF6 gene and decreased IRAK1 gene expressions in the peripheral mononuclear cells of patients with Sjogren's syndrome. *Immunol Lett* 2012;141(2):165-8.

- [56] LeRoy EC, Black C, Fleischmajer R, et al. Scleroderma (systemic sclerosis): classification, subsets and pathogenesis. *J Rheumatol* 1988;15(2):202-5.
- [57] Maurer B, Stanczyk J, Jungel A, et al. MicroRNA-29, a key regulator of collagen expression in systemic sclerosis. *Arthritis Rheum* 2010;62(6):1733-43.
- [58] Peng WJ, Tao JH, Mei B, et al. MicroRNA-29: a potential therapeutic target for systemic sclerosis. *Expert Opin Ther Targets* 2012;16(9):875-9.
- [59] Zhu H, Li Y, Qu S, et al. MicroRNA expression abnormalities in limited cutaneous scleroderma and diffuse cutaneous scleroderma. *J Clin Immunol* 2012;32(3):514-22.
- [60] Felson DT. The course of osteoarthritis and factors that affect it. *Rheum Dis Clin North Am* 1993;19(3):607-15.
- [61] Iliopoulos D, Malizos KN, Oikonomou P, Tsezou A. Integrative microRNA and proteomic approaches identify novel osteoarthritis genes and their collaborative metabolic and inflammatory networks. *PLoS One* 2008;3(11):e3740.
- [62] Jones SW, Watkins G, Le Good N, et al. The identification of differentially expressed microRNA in osteoarthritic tissue that modulate the production of TNF-alpha and MMP13. *Osteoarthritis Cartilage* 2009;17(4):464-72.
- [63] Tardif G, Hum D, Pelletier JP, Duval N, Martel-Pelletier J. Regulation of the IGFBP-5 and MMP-13 genes by the microRNAs miR-140 and miR-27a in human osteoarthritic chondrocytes. *BMC Musculoskelet Disord* 2009;10:148.
- [64] Li X, Gibson G, Kim JS, et al. MicroRNA-146a is linked to pain-related pathophysiology of osteoarthritis. *Gene* 2011;480(1-2):34-41.
- [65] Okuhara A, Nakasa T, Shibuya H, et al. Changes in microRNA expression in peripheral mononuclear cells according to the progression of osteoarthritis. *Mod Rheumatol* 2012;22(3):446-57.
- [66] Klareskog L, Catrina AI, Paget S. Rheumatoid arthritis. *Lancet* 2009;373(9664):659-72.
- [67] Kawano S, Nakamachi Y. miR-124a as a key regulator of proliferation and MCP-1 secretion in synoviocytes from patients with rheumatoid arthritis. *Ann Rheum Dis* 2011;70 Suppl 1:i88-91.
- [68] Kurowska-Stolarska M, Alivernini S, Ballantine LE, et al. MicroRNA-155 as a proinflammatory regulator in clinical and experimental arthritis. *Proc Natl Acad Sci U S A* 2011;108(27):11193-8.
- [69] Nakamachi Y, Kawano S, Takenokuchi M, et al. MicroRNA-124a is a key regulator of proliferation and monocyte chemoattractant protein 1 secretion in fibroblast-like synoviocytes from patients with rheumatoid arthritis. *Arthritis Rheum* 2009;60(5):1294-304.
- [70] Nakasa T, Miyaki S, Okubo A, et al. Expression of microRNA-146 in rheumatoid arthritis synovial tissue. *Arthritis Rheum* 2008;58(5):1284-92.

- [71] Niederer F, Trenkmann M, Ospelt C, et al. Down-regulation of microRNA-34a* in rheumatoid arthritis synovial fibroblasts promotes apoptosis resistance. *Arthritis Rheum* 2012;64(6):1771-9.
- [72] Niimoto T, Nakasa T, Ishikawa M, et al. MicroRNA-146a expresses in interleukin-17 producing T cells in rheumatoid arthritis patients. *BMC Musculoskelet Disord* 2010;11:209.
- [73] Stanczyk J, Ospelt C, Karouzakis E, et al. Altered expression of microRNA-203 in rheumatoid arthritis synovial fibroblasts and its role in fibroblast activation. *Arthritis Rheum* 2011;63(2):373-81.
- [74] Stanczyk J, Pedrioli DM, Brentano F, et al. Altered expression of MicroRNA in synovial fibroblasts and synovial tissue in rheumatoid arthritis. *Arthritis Rheum* 2008;58(4):1001-9.
- [75] Bluml S, Bonelli M, Niederreiter B, et al. Essential role of microRNA-155 in the pathogenesis of autoimmune arthritis in mice. *Arthritis Rheum* 2011;63(5):1281-8.
- [76] Worm J, Stenvang J, Petri A, et al. Silencing of microRNA-155 in mice during acute inflammatory response leads to derepression of c/ebp Beta and down-regulation of G-CSF. *Nucleic Acids Res* 2009;37(17):5784-92.
- [77] Pauley KM, Satoh M, Chan AL, Bubb MR, Reeves WH, Chan EK. Upregulated miR-146a expression in peripheral blood mononuclear cells from rheumatoid arthritis patients. *Arthritis Res Ther* 2008;10(4):R101.
- [78] Feng ZT, Li J, Ren J, Lv Z. [Expression of miR-146a and miR-16 in peripheral blood mononuclear cells of patients with rheumatoid arthritis and their correlation to the disease activity]. *Nan Fang Yi Ke Da Xue Xue Bao* 2011;31(2):320-3.
- [79] Li J, Wan Y, Guo Q, et al. Altered microRNA expression profile with miR-146a upregulation in CD4+ T cells from patients with rheumatoid arthritis. *Arthritis Res Ther* 2010;12(3):R81.
- [80] Murata K, Yoshitomi H, Tanida S, et al. Plasma and synovial fluid microRNAs as potential biomarkers of rheumatoid arthritis and osteoarthritis. *Arthritis Res Ther* 2010;12(3):R86.
- [81] Taganov KD, Boldin MP, Chang KJ, Baltimore D. NF-kappaB-dependent induction of microRNA miR-146, an inhibitor targeted to signaling proteins of innate immune responses. *Proc Natl Acad Sci U S A* 2006;103(33):12481-6.
- [82] Nakasa T, Shibuya H, Nagata Y, Niimoto T, Ochi M. The inhibitory effect of microRNA-146a expression on bone destruction in collagen-induced arthritis. *Arthritis Rheum* 2011;63(6):1582-90.
- [83] Yamasaki K, Nakasa T, Miyaki S, et al. Expression of MicroRNA-146a in osteoarthritis cartilage. *Arthritis Rheum* 2009;60(4):1035-41.

- [84] Fulci V, Scappucci G, Sebastiani GD, et al. miR-223 is overexpressed in T-lymphocytes of patients affected by rheumatoid arthritis. *Hum Immunol* 2010;71(2):206-11.
- [85] Sebastiani GD, Fulci V, Niccolini S, et al. Over-expression of miR-223 in T-lymphocytes of early rheumatoid arthritis patients. *Clin Exp Rheumatol* 2011;29(6):1058-9.
- [86] Szodoray P, Alex P, Chappell-Woodward CM, et al. Circulating cytokines in Norwegian patients with psoriatic arthritis determined by a multiplex cytokine array system. *Rheumatology (Oxford)* 2007;46(3):417-25.
- [87] Costello P, Bresnihan B, O'Farrelly C, FitzGerald O. Predominance of CD8+ T lymphocytes in psoriatic arthritis. *J Rheumatol* 1999;26(5):1117-24.
- [88] Fitzgerald O, Winchester R. Psoriatic arthritis: from pathogenesis to therapy. *Arthritis Res Ther* 2009;11(1):214.
- [89] Partsch G, Steiner G, Leeb BF, Dunky A, Broll H, Smolen JS. Highly increased levels of tumor necrosis factor-alpha and other proinflammatory cytokines in psoriatic arthritis synovial fluid. *J Rheumatol* 1997;24(3):518-23.
- [90] Alenius GM, Eriksson C, Rantapaa Dahlqvist S. Interleukin-6 and soluble interleukin-2 receptor alpha-markers of inflammation in patients with psoriatic arthritis? *Clin Exp Rheumatol* 2009;27(1):120-3.
- [91] Mortel MR, Emer J. Prospective new biologic therapies for psoriasis and psoriatic arthritis. *J Drugs Dermatol* 2010;9(8):947-58.
- [92] Sonkoly E, Wei T, Janson PC, et al. MicroRNAs: novel regulators involved in the pathogenesis of psoriasis? *PLoS One* 2007;2(7):e610.
- [93] Primo MN, Bak RO, Schibler B, Mikkelsen JG. Regulation of pro-inflammatory cytokines TNFalpha and IL24 by microRNA-203 in primary keratinocytes. *Cytokine* 2012.
- [94] Sonkoly E, Stahle M, Pivarcsi A. MicroRNAs: novel regulators in skin inflammation. *Clin Exp Dermatol* 2008;33(3):312-5.
- [95] Lerman G, Avivi C, Mardoukh C, et al. MiRNA expression in psoriatic skin: reciprocal regulation of hsa-miR-99a and IGF-1R. *PLoS One* 2011;6(6):e20916.
- [96] Meisgen F, Xu N, Wei T, et al. MiR-21 is up-regulated in psoriasis and suppresses T cell apoptosis. *Exp Dermatol* 2012;21(4):312-4.
- [97] Xu N, Brodin P, Wei T, et al. MiR-125b, a microRNA downregulated in psoriasis, modulates keratinocyte proliferation by targeting FGFR2. *J Invest Dermatol* 2011;131(7):1521-9.
- [98] Zibert JR, Lovendorf MB, Litman T, Olsen J, Kaczowski B, Skov L. MicroRNAs and potential target interactions in psoriasis. *J Dermatol Sci* 2010;58(3):177-85.
- [99] Ichihara A, Jinnin M, Yamane K, et al. microRNA-mediated keratinocyte hyperproliferation in psoriasis vulgaris. *Br J Dermatol* 2011;165(5):1003-10.

- [100] Ichihara A, Jinnin M, Oyama R, et al. Increased serum levels of miR-1266 in patients with psoriasis vulgaris. *Eur J Dermatol* 2012;22(1):68-71.
- [101] Chan EK, Satoh M, Pauley KM. Contrast in aberrant microRNA expression in systemic lupus erythematosus and rheumatoid arthritis: is microRNA-146 all we need? *Arthritis Rheum* 2009;60(4):912-5.
- [102] Tsitsiou E, Lindsay MA. microRNAs and the immune response. *Curr Opin Pharmacol* 2009;9(4):514-20.