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MicroRNAs in juvenile idiopathic arthritis: Can we learn more about pathophysiological mechanisms?

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ABSTRACT

Juvenile idiopathic arthritis (JIA) is a heterogeneous and multifactorial group of chronic arthritis with an onset before the age of 16 years. The pathogenesis of this disease is poorly understood, which makes the distinction among subtypes unclear, delays diagnosis and optimal therapeutic management. MicroRNAs (miRNAs) are small non-coding RNAs that play a critical role in the regulation of immune responses. Their expression is tightly controlled to ensure cellular homeostasis and function of innate and adaptive immune cells. Abnormal expression of miRNAs has been associated with the development of many inflammatory and autoimmune diseases. In this review, we gather results published on miRNAs expression profiles in JIA patients with the aim to identify miRNAs that can be used as diagnostic biomarkers and provide information on disease activity and progression. We also focus on miRNAs deregulated in different forms of JIA to shed light on common pathways potentially involved in disease pathophysiology.

1. Juvenile idiopathic arthritis

Juvenile idiopathic arthritis (JIA) is a heterogeneous group of chronic childhood arthritis persisting for > 6 weeks. JIA represents the most common rheumatic disease with an onset before the age of 16 years. The prevalence of this autoimmune disorder of unknown origin is between 16 and 150 cases per 100,000 children [1,2]. The International League of Associations for Rheumatology (ILAR) has identified 7 subtypes of JIA based on the number of affected joints, serologic features and the presence of systemic signs and symptoms [3]. Categories of JIA include oligoarticular JIA, rheumatoid factor (RF)-negative polyarticular JIA, RF-positive polyarticular JIA, systemic JIA (sJIA), enthesitis-related arthritis (ERA), psoriatic arthritis and undifferentiated JIA. The oligoarticular subtype characterized by four or fewer joints affected during the first 6 months of symptoms represents nearly 50% of cases in Europe, while polyarticular JIA with five or more arthritic joints accounts for 25 to 40% [4]. The other forms of JIA are less common in Europe. SJIA involves a fever lasting > 2 weeks that can be associated with generalized lymphadenophaty, evanescent erythematous rash, hepatomegaly, splenomegaly or serositis. Psoriatic arthritis is defined by the presence arthritis and psoriasis or some psoriatic features like nail pitting, onycholysis, dactylitis or psoriasis in a first-degree relative. ERA corresponds to arthritis supplemented with inflammation at the ligamentous or tendinous attachments to the bone. Finally, undifferentiated arthritis includes all forms of arthritis that does not fulfill any of the criteria mentioned above, or fits more than one category. This classification is still under revision and discussions continue on its robustness, as there is a lack of specific markers (clinical and/or biological) discriminating between JIA subtypes.

Little is known about the cause and pathophysiology of JIA. The literature describes JIA as a multifactorial disease for which some specific susceptibility genes have been identified [5]. They can be divided into two groups: HLA genes and non HLA-related genes. HLA class I (*HLA A-2* and *HLA B27*) and HLA class II (*HLADRB1* and *HLA DP*) alleles have been associated with JIA, indicative of a role of T lymphocytes in these diseases. Several non-HLA candidate genes have also been identified in JIA cases, including *MIF*, *PTPN22*, *SLC11A6*, *WISP3* and tumor necrosis factor (*TNF*)-α [6]. The autoreactive immune response in JIA is a consequence of a deregulation of innate and adaptive immunity, which is assumed to be triggered by an adaptive reaction towards self-antigens. Indeed, antigen-presenting cells like monocytes and dendritic cells (DCs) play a critical role in synovial inflammatory reaction [7–9]. Impairments in their distribution [10–12] as well as in their cytokine production [13–16] are described in cases of JIA. They are responsible for the accumulation of activated memory T cells in the joints [17], resulting in exacerbated immune response and tissue damage. While genetic specificities determine the susceptibility to develop the disease, the interaction with environmental features seems to be involved in the initiation of the autoimmune reaction. These environmental triggers are largely unknown and might include specific

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infectious agents or vaccinations. For example, after vaccination with meningoccocus C, some polyarticular JIA patients showed an increased proinflammatory immune response towards vaccine antigens [18]. Also, several reports show that JIA is more prevalent in rural than urban environments [19,20]. However, further work on large cohorts is needed to validate these hypotheses and to identify specific factors that contribute to the initiation and development of the pathology.

Epigenetic mechanisms are known to play a major role in the regulation of biological processes, including immune reactions. Over the past several years, a growing interest in microRNAs (miRNAs) has been shown. They regulate gene expression and it has become clear that alterations in their expression profiles can contribute to the development of pathological conditions like cancers and autoimmune diseases [21,22]. In 2007, the first evidence of a linkage between miRNAs and the pathogenesis of adult form of arthritis, rheumatoid arthritis (RA), was found [23]. Since then, the abnormal expression of multiple miRNAs has been documented in the blood and inflamed joints of RA patients, some of them reflecting the pathological state of tissues and disease activity [24–28]. Concerning juvenile arthritis, it was only in 2014 that the first report on miRNAs quantification was published [29]. The aim of the present review is to provide a state of the art of the findings on miRNAs in JIA and to document on their role in the pathogenesis of this heterogeneous group of diseases, as well as on their potential as biomarkers and therapeutic tools.

2. Overview of miRNAs in biological networks

MiRNAs are non-coding, endogenously generated and single-stranded RNAs of approximately 22 nucleotides. According to the latest miRNA database, 2588 miRNAs have been identified in humans [30]. They exhibit highly regulated patterns of expression, specific of each cell types and changing according to cellular differentiations [31]. MiRNAs predominantly act as negative regulators of the expression of target genes by translational repression or cleavage of messenger RNA (mRNA). Under certain conditions, miRNAs have been reported to up-regulate the translation of target mRNAs [32]. It is estimated that > 60% of human protein coding genes contain at least one miRNA binding site [30]. MiRNAs are essential for the maintenance of cellular homeostasis and normal function. They have a key role in many physiological systems [33,34], as they allow the rapid or transient change of gene expression profiles in response to intracellular or extracellular signals [35].

2.1. Biogenesis of miRNAs

The biogenesis of miRNAs starts in the nucleus where they are transcribed from genes, mainly by RNA polymerase II [30]. Some miRNA genes are transcribed individually, but a large fraction of them are present in the genome with expression patterns and arrangements that suggest they are transcribed as polycistronic primary transcripts [36]. The primary transcript of miRNA gene (pri-miRNA) is usually hundreds to thousands of nucleotides long and has one or more hairpin loop structures. MiRNA precursors can be processed either in a canonical or a non-canonical biogenesis pathway [37,38]. In the canonical miRNA pathway, the pri-miRNA is cleaved in the nucleus by the RNase III endonuclease Drosha, along with a double-stranded-RNA-binding protein called DiGeorge syndrome critical region protein 8 (DGCR8). The pri-miRNA then becomes a 60 to 70 nucleotides stem-loop intermediate called pre-miRNA. In the alternative pathway named non-canonical miRNA biogenesis, miRNA precursors designated as mirtrons do not contain the stem-loop structure and the flanking single stranded segments essential for the binding of the Drosha/DGCR8 microprocessor. Therefore, they bypass Drosha processing and go through a splicing of 5'cap and polyA tails after which they become pre-miRNAs and can enter the canonical miRNA processing pathway. The pre-miRNA is then exported from the nucleus into the cytoplasm by Exportin-5 and its RAN-GTP cofactor, where it is cleaved by RNase III Dicer and becomes an unstable, asymmetric miRNA/miRNA duplex of 19-22 nucleotides [30,39]. This duplex is composed of a guide RNA sequence and a passenger RNA. After the processing by an helicase, the guide sequence also called the active strand is selectively loaded into ribonucleoprotein (RNP) complexes to generate RNA-induced silencing complexes (RISC). This active strand incorporated in RISC is therefore able to act as a mature miRNA, while the passenger miRNA is usually released and rapidly degraded [30].

2.2. MiRNAs mode of action

After being loaded on RISC, the mature miRNA can interact with its target mRNA on complementary binding sites originally thought to be located only in 3′ untranslated regions (UTRs). Publications then showed that miRNAs are also able to interact with complementary sequences located on 5'UTR of mRNA, as well as on their promoter or coding sequence (CDS) regions [40–42]. These interactions involve a continuous and perfect base pairing of 2-8 nucleotides of the miRNA, representing the "seed" region. Target recognition is followed by the catalytic action of proteins forming the RISC complex. Among them, Argonaute (Ago) 2 has been found to cleave mRNA by endonuclease activity. Other proteins of the Ago family can induce mRNA deadenylation and inhibition of translation [30,43]. Alternatively, repressed mRNA may be accumulated in specific intracellular compartment called GW/P bodied, along with miRNAs and associated proteins [30].

While miRNA-mediated silencing mechanisms are well known, their actions as posttranscriptional upregulators are less documented. An emerging group of studies reveals that the degree of complementarity between miRNA and the target mRNA dictates the translation outcome [44–46]. Indeed, if perfect base pairing usually leads to mRNA cleavage or decay, partial base pairing can have a different effect on gene expression. Not only can it induce mRNA deanylation and translation silencing, but it might also up-regulate mRNA expression in response to specific sequences, cofactors or cellular conditions. Postranscriptional up-regulation can either be performed directly by miRNPs, or indirectly, after a regulatory effect on miRNA-mediated inhibition [47]. Vasudevan and his colleagues identified a translation activation of tumor necrosis factor-α (TNF-α) induced by miR-369-3p [32]. TNF-α is a cytokine playing an important role in immune reactions [48]. It appears that upon cell cycle arrest, the AU-rich elements (AREs) located on the 3'UTR of TNF-α mRNA become translation activation signals and recruit AGO2 and fragile X mental retardation- related protein 1 (FXR1) that are associated with miRNPs. This association is directed by miR-369-3p [32]. The versatility of miRNP function in response to specific cellular conditions has only recently begun to be characterized, and a deeper investigation of regulatory switches that dictate repression versus stimulation is required.

2.3. MiRNAs in body fluids

MiRNAs biogenesis and function is tightly regulated in every cell type. In some tissues, miRNAs show a specific and unique distribution profile. A regulation has also been observed concerning the expression of extracellular miRNAs. Circulating RNAs were identified for the first time in 1972 when intact RNAs were detected in plasma, suggesting that specific structures were preventing their degradation from ribonucleases [49]. Since then, miRNAs have been found in fluids such as serum, saliva and urine [50–52]. Weber and his team analyzed the expression of miRNAs in 12 human body fluids: plasma, urine, saliva, tears, breast milk, colostrum, amniotic fluid, bronchial lavage, pleural fluid, peritoneal fluid, cerebrospinal fluid and seminal fluid [53]. They identified similarities among several of them, like miRNA distribution in plasma and saliva, sign of existing exchanges between these two fluids. Amniotic fluid did not show resemblance with the other fluids tested, probably because of the filtration process occurring in the

placenta that limits the transport of molecules from the amniotic fluid to the rest of the body. Interestingly, the highest amounts of miRNA were found in tears. MiRNAs have also been detected in the synovial fluid (SF) of patients with arthritis [54].

Extracellular miRNAs are protected against enzymatic degradation by their inclusion in extracellular vesicles (exosomes, microparticules and apoptotic bodies), or their association with either RNA-binding proteins or lipoprotein structures [55]. Their stability allows them to be taken up by distant cells and therefore be involved in cell-to-cell communication. However, mechanisms controlling miRNA regulation and their release from cells are yet to be elucidated.

3. MiRNAs and the immune response

By the role they exert in the regulation of proliferation, maturation, differentiation and activation of immune cells, miRNAs are crucial for the function of both innate and adaptive immune systems [22,56–58]. The first evidence of miRNAs being involved in immune responses was reported in 2004, when Chen and his team identified 3 miRNAs (miR-142a, miR-181a and miR-223) expressed in specific mouse hematopoietic cells. They showed that the expression of these miRNAs is tightly regulated during hematopoiesis and lineage commitment, which allows them to efficiently participate in the control of immune system [59].

MiRNAs mode of action is highly efficient and versatile. Their capacity to induce rapid changes in gene expression makes them essential actors in the interplay between immune cells and pathogens [58,60,61]. Cells of the innate immune system, including granulocytes, monocytes and DCs, represent the first elements involved in the defense against invading microorganisms [62]. These cells express on their membrane pattern recognition receptors (PRRs) including tool-like receptors (TLRs), nucleotide-binding oligomerization domain (NOD)-like receptors (NLRs), C-type lectin-like receptors (CLRs) and retinoic acid-inducible gene (RIG)-I-like-receptors (RLRs). PRRs can recognize and bind to a wide range of pathogen- associated molecular patterns (PAMPs), which results in the triggering of intracellular signaling pathways that leads to the initiation of an inflammatory response [63,64]. Significant changes have been observed in the expression of various miRNAs in response to PAMPs or cytokines stimulation [65]. For example, lipopolysaccharide (LPS)-mediated inflammatory response is associated with the over-expression of miR-146a/b and miR-155, as well as miR-125b down-regulation in human monocytes. MiR-146 acts as a negative regulator of TLR4, TLR2 and TLR5 signaling pathways by inhibiting the translation of tumor necrosis factor receptor-associated factor 6 (TRAF6) and IL-1 receptor-associated kinase 1 (IRAK1) [66]. Antigens from bacteria and viruses can activate TLR4, TLR2, TLR3 or TLR9 on macrophages and induce an increase of miR-155 in these cells [66–68]. MiR-155 targets suppressor of cytokine signaling protein 1 (SOCS1), Fas-associated death domain protein (FADD), TNF receptor superfamily-interacting serine-threonine kinase 1 (Ripk1) and IkappaB kinase epsilon (IKKepsilon), which results in the up-regulation of TNF-α [67]. Moreover, this miRNA participates in the control of inflammatory cytokines production such as IL-1β during DCs activation [69]. Like miR-146a, the expression of miR-155 is associated with DCs maturation [69–71]. Finally, miR-125b directly binds to TNF-α transcripts to inhibit their translation. The lower expression of this miRNA is therefore in accordance with elevated levels of TNF- α [68].

Evidence of miRNAs significance in adaptive immunity became apparent after experiments in which Dicer was conditionally inactivated in mice T and B lymphocytes, thereby disrupting miRNA synthesis [72]. In immature thymocytes, Dicer depletion results in aberrant T cells development with reduced T cells number both in thymus and peripheral lymphoid organs, followed by impaired T helper (Th) cells differentiation and cytokines production [72,73]. Dicer-deficient B cell progenitors undergo a blocking at the pro- to pre-B cell transition affecting antibody production and diversity [74]. MiR-146a and miR-155 not only regulate innate immunity, they are also critical in the adaptive immune system. They represent two of the most studied miRNAs in autoimmune disorders like RA and illustrate the complex role of miRNAs in immune responses. Concerning miR-146a, an up-regulation of its expression has been observed in Th1, while it is down-regulated in Th2 cells [75]. MiR-146a shows high expression in regulatory T cells (Tregs) where it targets signal transducer and activator of transcription (STAT)-1 and therefore regulates Tregs-mediated suppression of interferon (IFN)-γ production by Th1 [76]. Evidence shows that miR-146a knockout in mice leads to an increase of the transcription of genes regulated by NF-κB, which in turns induces myeloid sarcomas and lymphomas development [77]. MiR-155 on the other hand targets c-maf, Pu.1 and activation-induced cytidine deaminase (AID), which are essential for lymphocyte homeostasis and normal function [78,79]. In miR-155 knockout mice, defective T- and B- mediated immunity is observed, including impaired Th1 and Th2 polarization with increased.

Th2 differentiation, lower number of Tregs cells, reduced germinal center response and decreased numbers of IgG class-switched cells [80–83].

Taken together, these data clearly illustrate the importance of miRNAs in the development of immune cells as well as in their function in innate and adaptive immune responses. Proper miRNAs expression is essential in order to avoid inappropriate inflammation or autoimmune reaction. Autoimmunity occurs when the immune system fails to recognize self antigens and trigger an immune response against them, which results in cellular and tissue damages [84]. Tolerance to autoantigens is ensured by checkpoints in central and peripheral lymphoid organs. Under normal circumstances, these checkpoints induce the destruction or silencing of autoreactive T and B lymphocytes [85]. The persistence of self-reactive cells in peripheral lymphoid tissues can provoke the development of autoimmune diseases. Immune tolerance breakdown is in some cases the result of a deregulation of miRNAs expression [86]. For example, experiments on mice indicated that miR-146a knockout in Treg cells disrupted immune tolerance mechanisms, resulting in the development of immune disorders [76]. Depending on autoimmune diseases, distinct mechanisms can be involved with specific deregulated miRNA expression patterns.

4. JIA and miRNAs

Since 2007, the literature gathers numerous studies on miRNAs dysregulated in the blood and inflamed joints of RA patients, which is the most common form of arthritis in adulthood [26,56,87–89]. It was not until 2014 that the first studies identifying miRNAs with altered expression in patients with JIA were published [29]. Analyses were mainly performed on serum and plasma samples, as well as on mononuclear cells isolated from blood samples (Table 1). The following sections gathers data on miRNAs that are abnormally expressed in JIA, comparing them with results obtained on healthy donors and RA patients. The study of miRNAs deregulated in JIA and RA allow the identification of disturbed mechanisms shared by two different forms of rheumatic disorders, while miRNAs with impaired expression only in JIA samples reveal information on pathways specifically involved in JIA pathogenesis.

4.1. MiRNAs from body fluids

4.1.1. MiRNA markers in serum

Kamiya et al. performed a real-time RT-PCR to quantify the expression of miR-223, miR-146a, miR-155, miR-132 and miR-16 in the serum of children with sJIA, polyarticular JIA and healthy donors. Their aim was to investigate the potential of these circulating miRNAs as disease biomarkers that could replace invasive biopsy [90]. They showed that miR-223 is significantly up-regulated in sera of patients in the active phase of JIA compared to inactive phase and healthy

Table 1
List of miRNAs differentially expressed in JIA compared to healthy controls.

Localization	Up–regulation	Down–regulation
Serum	miR–223 [90][a]	
Plasma	miR–16 [98]	
	miR–26a [98] [a]	
		miR–132 [98][a]
	miR–146a [98]	
	miR–145 [98]	
		miR–155 [98]
	miR–223 [98]	
PBMC	miR–16 [117][a]	
		miR–19a [108]
		miR–21 [108][a]
	miR–99a [117]	
	miR–100 [117]	
	miR–125a [117]	
		miR–133a [117]
	miR–146a/b [108,117][a]	
	miR–150 [108,117][a]	
	miR–155 [29][a]	
	miR–181c [117]	
	miR–223 [117][a]	

[a] Also abnormally expressed in rheumatoid arthritis.

controls. They also found that levels of miR-223 are correlated to erythrocyte sedimentation rate (ESR) and matrix metalloproteinase-3 (MMP-3) in polyarthritis, and associated to ESR in sJIA. As mentioned above, miR-223 has a crucial role in the regulation of the differentiation of myeloid cells. It has been reported that miR-223 is also elevated in RA sera compared to healthy donors and is involved in the differentiation of osteoclasts, therefore impacting on joint erosion [91]. Filkova and her team revealed that the high expression of miR-223 in the serum of RA patients is linked to C-reactive protein (CRP) levels [92]. Thus, in JIA as in RA, serum miR-223 levels are considered as potential biomarkers for disease activity [90,92].

Kamiya et al. also quantified miR-146a and miR-155 expression in JIA sera. As previously specified, these two miRNAs display important functions in the immune system. However, no significant difference was observed in the serum expression of these two miRNAs between JIA patients and healthy subjects [90]. MiR-155 expression levels were slightly higher in the serum of sJIA than in polyarticular serum. Moreover, a correlation was detected between serum miR-146a and MMP-3 in polyarticular JIA patients. Contrary to JIA, studies in RA sera have reported a higher expression of miR-155 in healthy controls than in RA patients [92,93]. MiR-155 as well as miR-146a concentrations in RA serum increase during disease progression and become significantly different in established RA compared to early cases of RA [92].

The quantification of miR-132 expression in JIA sera showed an increase in sJIA compared to polyarticular JIA. No significant changes were observed compared with healthy controls [90]. MiR-132 is known for its anti-inflammatory effect as it targets p300 transcriptional co-activator and inhibits the expression of IFN-β, Interferon-stimulated gene 15 (ISG15), Interleukin (IL)-1β and IL-6 [94]. Kamiya et al. did not find any correlation between miR-132 and MMP-3 or ESR. Similar results were obtained in RA studies, with the same levels of miR- 132 between patients and healthy individuals, as well as an absence of association between the expression of this miRNA and disease activity [92].

Finally, Kamiya et al. could not evidence differences in miR-16 expression between sJIA, polyarticular JIA and healthy donors [90]. However, they reported a mild correlation of miR-16 with MMP-3 in both forms of JIA. Among other functions, this miRNA is involved in apoptosis by targeting B-cell lymphoma 2 (Bcl-2) [95]. It has also been studied in RA patients, where reports show that it targets TNF-α [96]. Serum levels of miR-16 in early RA are low and increase with the progression of disease [92]. Like miR-223 expression in serum, miR-16 level might be a predictor for disease outcome in case of RA [97].

4.1.2. MiRNA markers in plasma

Ma et al. quantified the expression of the five same miRNAs (miR-223, miR-146a, miR-155, miR-132 and miR-16) in the plasma of children suffering from oligoarticular JIA, polyarticular JIA, juvenile ankylosing spondylitis (JAS) as compared with healthy subjects [98]. Using a microarray analysis, they selected these miRNAs because of their differential expression between groups and performed a validation study using quantification by RT-qPCR. Their aim was to identify novel biomarkers for JIA that are correlated with specific disease characteristics. Analyses revealed an up-regulation of miR-16, miR-146a and miR-223 levels in oligo- and poly-arthritis compared to JAS and healthy donors. Moreover, miR-16 was more elevated in polyarticular JIA than in the oligoarticular subtype. Concerning miR-132 and miR-155, they were down-regulated in polyarthritis compared to JAS and healthy individuals. Results with oligoarthritis showed that miR-132 was under-expressed in JIA compared with controls and JAS, while miR-155 is higher in healthy donors and equally expressed in JAS and oligoarthritis.

Ma et al. also considered clinical variables and cytokine concentrations in order to evaluate the potential of plasma miRNAs as markers of JIA progression. They found that miR-16 expression levels correlate with Juvenile Arthritis Magnetic Resonance Imaging Score (JAMRIS) on the hip (JAMRIS-hip) and with the 27-joints Juvenile Arthritis Activity Score (JADAS-27). MiR-146a was correlated with JAMRIS-hip, the limited joint count (LTC) and the 10-joints/27-joints/71-joints JADAS (JADAS-10/27/71). Cytokines analysis indicated a positive correlation of plasma miR-16 and IL-6 concentration, while a negative correlation was observed between miR-146a and TNF-α. Down-regulation of TNF-α by miR-146a is well described, as this miRNA targets TRAF6 [66]. MiR-16 has been reported to modulate LPS-induced production of IL-6, IL-1α and IL-8 via the targeting of silencing mediator for retinoid and thyroid hormone receptor (SMRT) [96,99]. These results suggested that expression levels of miR-146a and miR-16 in JIA plasma might be considered as potential markers for disease activity. Ma et al. could not find any relevant correlation between biological or clinical parameters of patients and miR-155, miR-132 or miR-223 expression in plasma.

Studies in RA plasma did not show any difference between miR-16, miR-223 and miR-155 expression between RA patients and healthy subjects, while miR-132 has been reported to be down-regulated in RA plasma compared to controls [54]. There are some conflicting results concerning miR-146a expression in RA plasma. Murata et al. identified an equal expression between RA and controls [54], while Wang et al. demonstrated that miR-146a is more expressed in plasma samples of healthy subjects as compared to established RA [93]. This discrepancy can be explained by variations in type of samples, patients medical history, disease progression, as well as differences in the sensitivity of methods used for miRNAs quantification. Murata et al. also analyzed miRNAs expression profile in SF and they found similar levels of miR-155 in plasma and SF of RA patients, while miR-16, miR-223, miR-132 and miR-146a were up-regulated in their plasma. Concerning clinical variables, they identified an inverse correlation between tender joint counts (TJC) and plasma miR-16, miR-223, miR-146a and miR-155. Plasma miR-16 was also inversely correlated to disease activity score of 28 joints (DAS28) index. Contrary to their expectation, no correlation was observed between SF miRNAs expression and disease activity [54]. Like in JIA, the usefulness of plasma miR-16 as a biomarker for disease activity in RA is highlighted [87,98].

Using a microarray profiling followed by a RT-qPCR, Sun and his team selected 4 miRNAs (miR-26a, miR-145, miR-181a and miR-1237) differentially expressed between sJIA plasma and healthy controls [100]. They compared their expression levels to those from other rheumatic diseases in order to identify miRNAs specific of sJIA. Their results indicated that miR-26a and miR-145 were up-regulated in sJIA

plasma in comparison to healthy subjects as well as patients with JAS, systemic lupus erythematosus (SLE), Kawasaki disease (KD) and Henoch-Schönlein purpura (HSP). The two other miRNAs (miR-181a and miR-1237) had irregular expressions in the four rheumatic disorders and were not JIA-specific. Sun et al. were particularly interested in miR-26a expression as this miRNA was specifically up- regulated in sJIA plasma and less expressed in oligo- and poly-arthritis. MiR-26a is involved in the regulation of cell proliferation and differentiation [101]. It has an anti-inflammatory action as it inhibits osteoclast formation and it has been reported to reduce arthritis severity in rats by targeting TLR-3 on their macrophages [102,103]. High expression of this miRNA is also observed in RA plasma compared to controls [87]. Sun et al. hypothesized that miR-26a in the plasma could be a marker for inflammatory severity in sJIA patients as there is a positive correlation between its expression and IL-6 plasma levels. This cytokine is highly produced during peaks of fever that occur often in sJIA [104]. Concerning other clinical variables like ESR, CRP, TJC or swollen joint count (SJC), no correlation was observed in sJIA or RA patients [100,105].

Although miR-145 expression in JIA plasma was not studied in depth by Sun et al., their team showed that this miRNA is up-regulated in oligoarticular JIA compared to polyarticular JIA, sJIA and healthy controls [100]. A study on RA synovial fibroblasts showed that miR-145 targets semaphorin 3A (SEMA3A) and therefore promotes the positive action of VEGF on survival, migration and invasion of fibroblast-like synoviocytes [106]. Another report highlights the role of miR-145 in chondrocyte homeostasis regulation and describes the potential involvement of this miRNA in cartilage destruction in osteoarthritis (OA) [107]. These functions have not been however studied so far in the context of JIA.

4.2. Intracellular miRNAs

Studies have been conducted on miRNAs isolated from all peripheral blood mononuclear cells (PBMC) in JIA patients. RT-qPCR analyses revealed that miR-21 and miR-19a levels are down-regulated in sJIA PBMC compared to healthy controls [108]. MiR-21 plays a key role in the triggering of inflammation and participates in the maturation and differentiation of T lymphocytes [109,110]. This miRNA down-regulates Bcl16 and promotes the activation of STAT3, which is a transcription factor involved in Th17 cells differentiation [111]. Studies in RA patients showed that miR-21 gene expression levels are also low [111]. They further indicated that the expression of STAT5 and phosphorylated STAT5 proteins decreased when STAT3 expression was activated. Mir-19a negatively regulates TNF-α and SOCS3 expression and increases IFN-α and STAT3 transduction [108,112]. The reduced expression of miR-19a in sJIA PBMC seems to be responsible for the high expression levels of SOCS3, TNF-α and IL-6 observed by Li et al. (2016). A report shows that miR-19a is down-regulated in RA synovial cells where it regulates TLR2 expression [112]. Altogether, Li et al. (2016) results indicate that miR-19a and miR-21 are involved in JAK/STAT signaling pathway and might participate in its activation [108].

Lashine et al. (2014) characterized miR-155 expression in PBMC of juvenile SLE, juvenile familial Mediterranean fever (FMF) and RF-positive polyarticular JIA patients. They observed an increase of miR-155 expression in JIA PBMC compared to healthy controls, while a down-regulation of this miRNA was identified in SLE and FMF patients in comparison to controls. It has previously been reported that miR-155 is a regulator of cyclic adenosine monophosphate (cAMP) regulatory element binding protein (CREB) mRNA expression [113]. The activation of CREB increases protein phosphatase 2A (PP2Ac) levels. This protein is involved in several immune pathogenesis via the regulation of IL-2 and IL-17 levels [114,115]. However, Lashine et al. could not detect any significant difference between PP2Ac expression in JIA PBMC compared to healthy PBMC. MiR-155 expression level in JIA PBMC is comparable to the level in RA PBMC. Indeed, increased concentrations are observed in both diseases compared to PBMC of healthy donors [116].

A study on miRNAs expression in blood monocytes revealed that miR-125a-5p and miR-181c are elevated in the active phase of sJIA compared to inactive sJIA and healthy controls [117]. Authors also analyzed miR-125a-5p in monocytes of polyarticular JIA patients and identified a low expression level, similar to the one in the inactive phase of sJIA. MiR-125a-5p and miR-181c are involved in monocytes polarization and regulate the expression of cytokine genes in macrophages [118,119]. Do and his team studied the effect of these two miRNAs on CD163, a scavenger receptor with anti-inflammatory function, which is expressed on myeloid cells [120,121]. Their results indicate that miR-181 family directly targets CD163 mRNA for degradation, while miR-125a-5p acts indirectly, by down-regulating IL-10 receptor subunit alpha (IL-10RA), which is necessary for IL-10-mediated expression of CD163. To our knowledge, these miRNAs have never been characterized in RA blood monocytes. However, a report shows that miR-125a-5p levels are increased in RA plasma and can activate NF-κB signaling pathway in B cells [105,122]. MiR-181 has been studied in other autoimmune disorders like primary Sjögren syndrome, where an up-regulation is observed in patients PBMC [123], as well as in psoriasis cases, where a down-regulation of its expression in PBMC is identified [124].

Levels of miR-146a/b and miR-150 were quantified in sJIA monocytes [108,117]. Results indicate that their expressions are more elevated in sJIA than in controls PBMC. These microRNAs are well characterized in RA PBMC where they are up-regulated compared to healthy donors [125,126]. A study on $CD14^{+}$ primary monocytes and human THP-1 cell line revealed that miR-146a induces a decrease in M1-type macrophage markers including IL-12, IL-6, CD86, TNF-α and iNOS, while it increases the expression of M2-type macrophage markers such as CCL12, CCL22, Arg1 and CD206 [108]. MiR-150 plays an important role in hematopoietic cell differentiation and regulates macrophages inflammatory response [127,128]. This non-coding gene has been shown to promote endothelial cells and monocytes migration by targeting CXCR4 [129,130]. Elevated levels of miR-146b and miR-150 in RA have been associated with infiltration of IL-17 cells, which exerts their pro- inflammatory role in the synovium [126].

Mir-16 and miR-223 are up-regulated in sJIA monocytes compared to controls [117]. MiR-16 has been reported to be associated with high levels of ferritin in sJIA patients. This miRNA is also over-expressed in RA PMBC where it is correlated to CRP values, ESR and TJC [92,116]. Concerning miR-223 expression in RA PBMC, it seemed to be moderately elevated [54]. This miRNA is often located in sites of inflammation as well as in peripheral circulation of RA patients [87].

Schulert and his team highlighted a difference of the expression of miR-99a, miR-100 and miR-133a between monocytes from patients with new-onset of sJIA and children with established sJIA, with a higher expression of miR-99 and miR-100 in active established arthritis and a down-regulation of miR-133a compared to controls [117]. They hypothesized that these miRNAs are involved the immune dysregulation observed in sJIA. The literature shows that miR-99a and miR-99b target mTOR, which is involved in cell proliferation and differentiation [131]. By targeting bone morphogenetic protein receptor type II (BMPR2), miR-100 has been suggested to exert a negative effect on osteogenic differentiation [132]. MiR-99a and miR- 100, both from the same miRNA family, have been reported to promote a Treg differentiation and to down-regulate Th17 polarization [133]. A study on RA and OA macrophages showed that the expression of miR-99a and miR-100 is higher in OA patients [134]. In the blood, miR-99 expression is slightly higher in RA patients than in healthy controls, while miR-100 reaches statistical difference and is over-expressed in RA blood [135]. Concerning miR-133a, an involvement in the regulation of inflammasome activation has been described [136]. Indeed, this work showed that the over-expression of miR-133a increases the cleavage of Caspase-1 p10 and IL-1β p17. This cleavage is followed by the suppression of mitochondrial uncoupling protein 2 (UCP2). Moreover, this miRNA

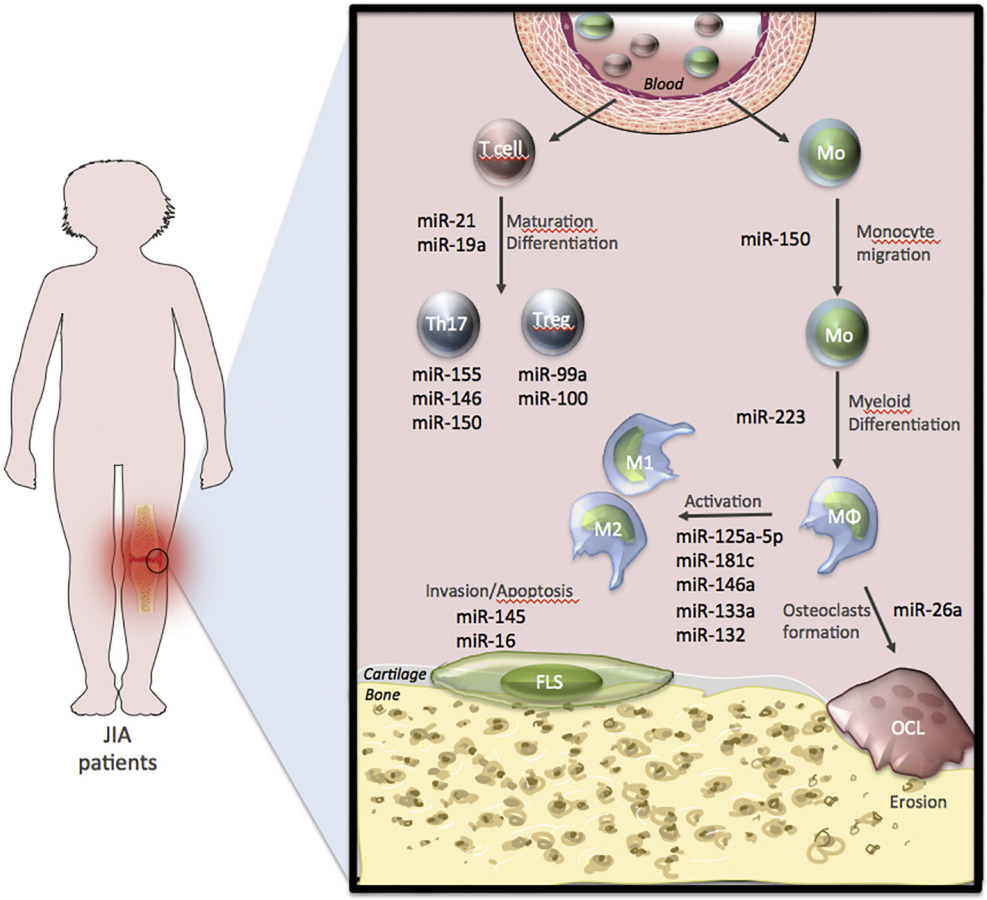

Fig. 1. Mechanisms targeted by miRNAs deregulated in JIA that might be involved in disease pathophysiology. Myeloid, lymphoid cells and fibroblast-like synoviocytes (FLS) are known to have a prominent role in JIA pathophysiology. Aberrant expression of miRNAs has an impact not only on the cells containing these non-coding genes, but also on surrounding cells. They can affect their functions and lead to imbalanced immune responses. MiR-21 and miR-19a participate in the maturation and differentiation of T lymphocytes. The down-regulation of their expression observed in JIA might lead to Th17 accumulation and thus to inflammatory reaction. Th17 polarization may be further promoted by the up-regulation of miR-155, miR-146 and miR-150, as their expression has been correlated to IL-17 levels. MiR- 99a and miR-100 positively regulate Treg differentiation. Therefore, over expression of these miRNAs might impact Treg frequencies in JIA joints. Concerning monocytes, miR-150 and miR-223 target genes involved in their migration and differentiation. Their up-regulation in JIA might promote monocyte migration to the joints. The abnormal expression of miR-125a- 5p, miR-181c, miR-146a, miR-133a and miR-132 might disturb the polarization of macrophages infiltrating JIA joints towards pro- versus anti-inflammatory activation, or apoptosis response. Up-regulation of miR-26a might reduce inflammation and osteoclast formation to counteract local pathogenic events. Finally, the over-expression of miR-145 and miR-16 may be involved in the survival, migration and invasion of FLS, as well as in their apoptosis.

targets Runt-related transcription factor 2 (Runx2), a protein essential for osteoblast differentiation and therefore bone formation [137]. MiR-133a is also down-regulated in fibroblasts isolated from OA than in RA [138]. Further studies aiming to determine the role of miR-99a, miR-100 and miR-133a in JIA and RA pathogenesis are required.

5. Conclusions

JIA includes a complex and heterogeneous group of childhood rheumatisms involving immune impairments, many remaining to be elucidated. Studies have tried to characterize the pathophysiological mechanisms responsible for JIA. Over the past few years, reports on miRNAs in the immune system regulation have brought to light several pathways deregulated in autoimmune disorders. So far, JIA studies have investigated miRNAs levels in blood and shown that they represent potential indicators of early disease events. They might therefore be used as diagnosis biomarkers. Since modulation of miRNAs expression also reveals information concerning mechanisms responsible for disease development and progression, we have used miRNAs described in JIA blood to highlight pathways that might be involved in disease pathophysiology (Fig. 1).

This review highlights mechanisms shared by JIA and RA, with miRNAs commonly deregulated in these two rheumatic disorders. With miR-223 highly expressed in the serum of patients, impairing the differentiation of myeloid cells and leading to immune system deregulation, as well as miR-26a, which is up-regulated in plasma and regulates osteoclasts formation, two pathways responsible for the bone erosion observed in these diseases are potentially identified. The down-regulation of an anti-inflammatory miRNA such as miR-132 in JIA and RA plasma participates to the exacerbated inflammation in the joints. T lymphocytes have been reported to play a key role in the pathogenesis of autoimmune disorders like JIA [139]. It is therefore not surprising to detect abnormal expression of miR-21 in JIA and RA PBMC, as it is a miRNA involved in the regulation of T cells maturation and differentiation. In the same manner, miR-155, miR-146 and miR-150, which are deregulated in JIA and RA PBMC, have been associated to IL-17 accumulation, a cytokine produced by Th17 cells. Impairments in monocyte functions are highlighted with the aberrant expression of miR-150 expression that deregulates their migration. Some miRNAs are correlated to disease activity and can thus be used as predictors of disease outcome. It is the case for miR-16 expression in the plasma and PBMC of patients, as well as miR-223 levels in serum and PBMC.

Interestingly, several miRNAs are only deregulated in JIA, while having similar expression in RA and healthy controls. Indeed, miR-16, miR-223 and miR-155 expression is the same in RA and healthy plasma, when miR-16 and miR-223 are increased in JIA, and miR-155 is down-regulated in comparison to controls. These miRNAs differentially expressed between two rheumatic diseases represent potential diagnosis biomarkers. Moreover, the identification of miRNAs with aberrant expression specifically in JIA patients will help to understand JIA pathophysiology. Indeed, this disorder involves mechanisms and consequences that are different from the adult form of arthritis as JIA patients have a maturing skeleton with incomplete ossification, as well as an immune system that is still undergoing modifications. Levels of miR-145 in JIA plasma, as well as miR-19a, miR-125a-5p, miR-181c, miR-99a, miR-100 and miR-133a in PBMC from JIA patients are deregulated. To our knowledge, the expression of these miRNAs has not been characterized in the same biological compartments for RA

patients. Therefore, data are insufficient to perform a comparison with JIA patients.

Not only are miRNAs essential for the understanding of the immune deregulation occurring in JIA and the diagnosis of this disease, they can also be useful for the prediction of the response to treatments and the development of therapies. However, further studies are needed to characterize miRNAs expression in JIA joints and elucidate their role in the pathogenesis of this disease. Moreover, before considering a therapeutic application, it is necessary to decipher molecular mechanisms and pathways regulated by these non-coding genes.

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