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Review

The role of microRNAs in the pathogenesis of autoimmune diseases

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ABSTRACT

MicroRNAs (miRNAs) are single-stranded, endogenous non-coding small RNAs, ranging from 18 to 25 nucleotides in length. Growing evidence suggests that miRNAs are essential in regulating gene expression, cell development, differentiation and function. Autoimmune diseases are a family of chronic systemic inflammatory diseases. Recent findings on miRNA expression profiles have been suggesting their role as biomarkers in autoimmune diseases such as systemic lupus erythematosus, rheumatoid arthritis and Sjögren's syndrome. In this review, we summarize the characteristics of miRNAs and their functional role in the immune system and autoimmune diseases including systemic lupus erythematosus, primary Sjögren's syndrome, rheumatoid arthritis, systemic sclerosis, multiple sclerosis and psoriasis; moreover, we depict the advantages of miRNAs in modern diagnostics.

Contents

1. Introduction

MicroRNAs (miRNAs) constitute a recently discovered family of small RNAs, ranging from 18 to 25 nucleotides in length. They are single-stranded, endogenous non-coding RNAs playing critical roles in regulating gene expression [1,2].

miRNAs regulate approximately 90% of protein-coding genes, and play a central role in various biological processes including immune call lineage commitment, differentiation, proliferation, apoptosis and maintenance of immune homeostasis. It is not surprising that alterations in the expression of miRNAs potentially contribute to the

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development of certain pathological conditions and clinical disorders. Nowadays, the pathogenetical role of miRNAs is most intensively studied in malignant diseases as well as autoimmune conditions. Changes in miRNA expression profiles have been identified in different autoimmune diseases such as systemic lupus erythematosus (SLE), rheumatoid arthritis (RA) and Sjögren's syndrome (SS) [3–5]. In this review, we summarize the characteristics of miRNAs and their functional role in the immune system and autoimmune diseases including SLE, primary SS, RA, systemic sclerosis (SSc), multiple sclerosis (MS) and psoriasis.

2. The biology of miRNAs

The majority of miRNA genes derived from the intergenic regions or in oriented antisense to form independent transcription units. Most of the others reside in the intron region of protein-coding genes [6]. Human miRNAs are not always genomically isolated; sometimes several miRNAs are assembled as clusters for further transcription and expression [7].

The miRNA biogenesis and maturation occur first in the nucleus and then in the cytoplasm with the help of several proteins and enzymes (Fig. 1). The first step in the miRNA biogenesis is the generation of primary miRNA transcripts (pri-miRNAs) from DNA molecules in the nucleus of the cell. Most miRNA genes are transcribed by RNA polymerase II to produce a few hundred to thousand nucleotide-long pri-miRNA [6]. The pri-miRNAs are both capped and polyadenylated with a typical hairpin structure [8]. These pri-miRNAs are recognized by an enzyme–protein complex and further cleaved into 70–100 nucleotide-long precursor miRNA (pre-miRNA). This complex is composed of Drosha and DiGeorge syndrome critical region gene 8 (DGCR8) and denoted as microprocessor complex [9]. Drosha is one of the two members of the RNase III family while DGCR8 is the double-stranded RNA-binding protein which is deleted in DiGeorge syndrome [10]. The pre-miRNA then exported to cytoplasm through exportin 5, which is a member of the karyopherin family of nucleocytoplasmic proteins. The exportin 5 recognizes a two-nucleotide overhang left by Drosha at the 3′ end of the pre-miRNA hairpin, requiring the GTP-bound form of the Ran GTPase for providing energy [11].

The noncanonical miRNA biogenesis pathway bypasses the microprocessor complex cleavage processing for another sort of pre-miRNAs, known as mirtrons, which directly spliced out of introns by spliceosome. The branched pre-mirtrons then undergo lariat-mediated debranching to mimic the structural features of pre-miRNAs [12,13]. Interestingly, mirtrons can not only be found in *Caenorhabditis elegans* and Drosophila, but also reported in mammals [14].

The pre-miRNAs have further processing to yield mature miRNA in the cytoplasm. The second member of the RNase III family named Dicer interacts with both 5′ and 3′ ends of the pre-miRNA and cleaves the hairpin loop, processing to a 19–25 nucleotides miRNA/miRNA* duplex [15,16]. The miRNA* was regarded as passenger strand since it is less-stable, while the miRNA as guide strand. The miRNA/miRNA* duplex releases the helix structure after loaded into the argonaute (Ago) proteins. The guide strand remains the interaction with Ago to generate the RNA-induced silencing complex (RISC), which facilitate miRNAs binds to their targets [17]. The passenger strand as complementary strand of the guide strand is degraded as a RISC complex substrate. However recent study demonstrates that several miRNA* are stably expressed and may play an important role, as well [18].

The mature miRNA interacts with the 3′-UTR of specific messenger RNA (mRNA) to regulate gene expression. Target mRNA is recognized by the 2–7 nucleotides of the 'seed' region of the miRNA [19]. The complementary degree of the base pairing between the miRNA seed region and mRNA defines the mechanism of gene regulation [20]. When the complementary base pairing is perfect or near-perfect, Ago protein of the RISC complex induces the endonucleotic cleavage of the target mRNA resulting in deadenylation and degradation of mRNA fragments. When the base pairing is incomplete, the formation of double-stranded RNA, resulting from the binding of miRNA, leads to translational repression [2,21,22]. Repressed mRNAs aggregate in cytoplasmic foci called P-bodies, which are known sites of mRNA destabilization [23,24].

3. miRNAs in immune system

The miRNAs play critical roles not only in the development of immune system but also the regulation of both innate and adaptive immunity [5,25]. MiRNAs function as translational repressors during stem cell fate and differentiation [26]. MiR-181, miR-223 and miR-142s are strongly expressed in hematopoietic cells and shown regulatory roles during hematopoietic lineage differentiation [27,28].

3.1. Innate immunity

The innate immune system is the first line of host defense and important in mechanisms against invading microorganisms; moreover, it forms the basis of the development of adaptive immunity. Host cells express diverse pattern recognition receptors (PRRs), including toll-like receptors (TLRs), C-type lectin-like receptors (CLRs), retinoic acid-inducible gene (RIG)-I-like-receptors (RLRs) and nucleotide-binding oligomerization domain (NOD)-like receptors (NLRs). These can recognize a wide range of pathogen-associated molecular patterns (PAMPs). These mechanisms trigger the intracellular signaling pathways, which results in releasing of proinflammatory cytokines, chemokines, and interferons (IFNs), as well as lead to the expression of co-stimulatory molecules [29]. TLRs are the most characterized PRRs, which are capable of potently activating different cell types, which could be highly expressed on most immune cells [30]. Their downstream signaling pathways lead to the production of a wide range of immune-stimulatory cytokines and chemokines. Aberrant activation of TLRs may result in unrestricted inflammatory responses therefore the family of TLRs may play a pivotal role in the development of autoimmune diseases [31]. Among all ten TLR subtypes, TLR1, TLR2, TLR4, TLR5, TLR6 and TLR10 are generally regarded as extracellular receptors, while the family of TLR3, TLR7, TLR8 and TLR9 are intracellular receptors located in endosomal compartments and responsible for the recognition of nucleic acids derived from viruses, bacteria and the host [32–35]. TLR4 can recognize lipopolysaccharides (LPSs), which is the typical endotoxin for gram-negative bacteria. The LPS-mediated inflammatory responses consequently induce overexpression of miR-146a/b, miR-132 and miR-155. Upregulation of miR-146 leads to translational repression of its target genes interleukin-1 receptor-associated kinase (IRAK) 1 and tumor necrosis factors receptor associated factor (TRAF) 6 [36]. miR-146 was recognized as a negative regulator of RLRs in the *in vitro* model of mouse macrophages through targeting IRAK1, IRAK2 and TRAF6 [37]. Exposure to LPS stimulates tumor necrosis factors (TNF)-α secretion. Overexpression of miR-155 and lower expression of miR-125b may relate with elevated level of TNF-α. It was indicated that miR-155 targets transcript coding gene for several proteins enhancing TNF-α translation, including Fas-associated death domain protein (FADD), IkappaB kinase epsilon (IKKepsilon) and TNFR superfamily-interacting serine–threonine kinase 1 (Ripk1), while miR-125b targets the 3′-UTR of TNF-α transcripts [38]. In miR-147 knockout mice, increased inflammatory cytokine expression found in macrophages upon TLR stimulation such as ligands to TLR2, TLR3 and TLR4. Thus miR-147 was regarded as a negative regulator in TLR-activated inflammatory responses [39]. The miR-1303 production is also regulated by the NF-κB pathway. A recent study revealed negative regulation of mycobacteria-induced Atg2B protein production related with autophagy process [40].

The miR-146a and miR-155 influence IFN-type I synthesis in plasmacytoid dendritic cells mediated by TLR-7 and TLR-9, while in T and B cells, group of miRNAs including miR-21, miR-126, miR-146a, miR-155, miR-1246 and others might correlate with epigenetic

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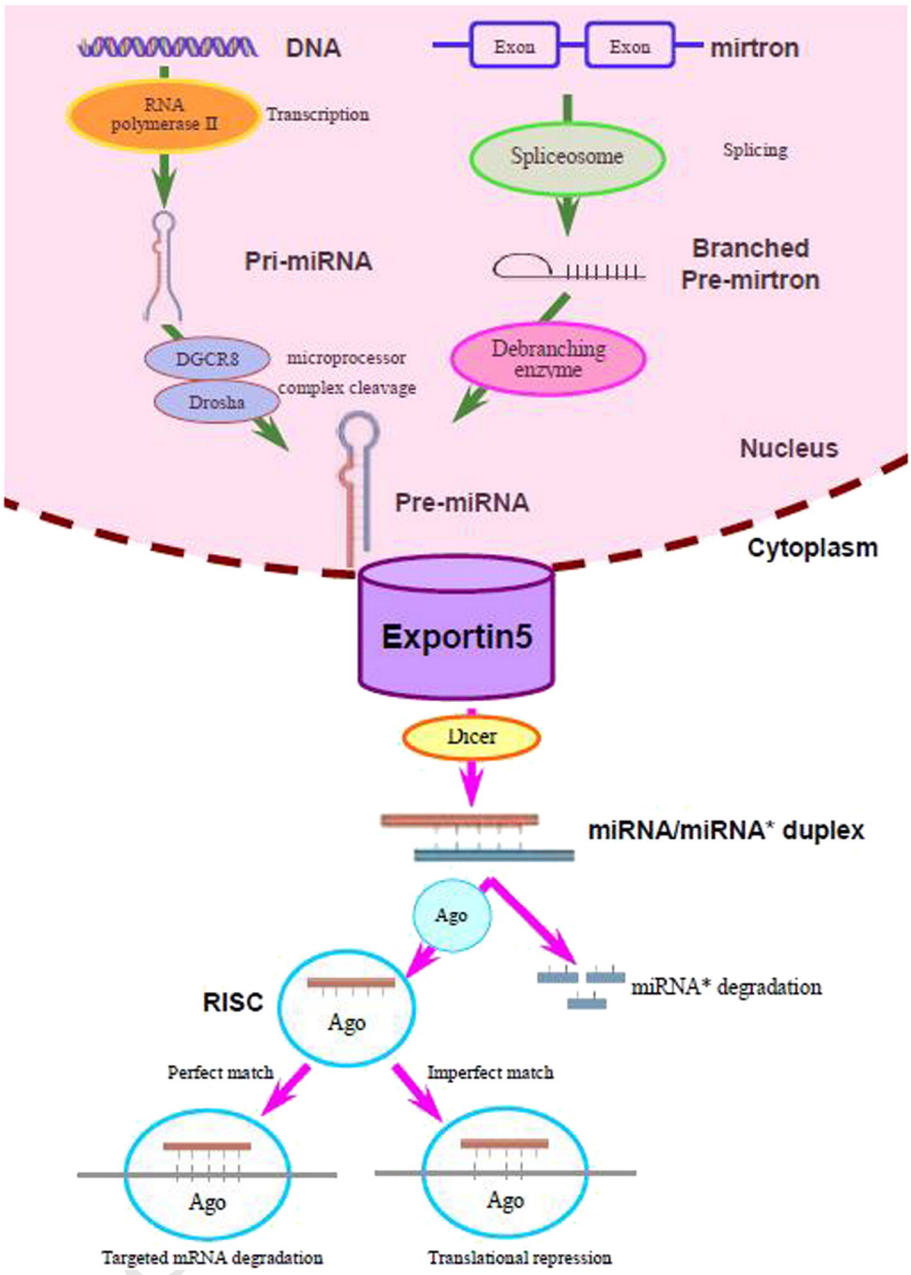

Fig. 1. microRNA biogenesis and mechanisms of action. Most miRNA are transcribed from genomic DNA by RNA polymerase II to generate typical hairpin structured primary miRNA transcripts (pri-miRNAs). These pri-miRNAs are recognized by the microprocessor complex (Drosha and DGCR8) and further cleaved into precursor miRNA (pre-miRNA). The noncanonical miRNA biogenesis pathway starts from mirtrons, which directly spliced out of introns by spliceosome. The branched pre-mirtrons then undergo lariat-mediated debranching to mimic the structural features of pre-miRNAs. The pre-miRNA then exported to cytoplasm through exportin 5. The pre-miRNA is further cleaved by Dicer into miRNA/miRNA* duplex. The guide strand loaded into the argonaute (Ago) proteins to generate the RNA-induced silencing complex (RISC), while the passenger strand (miRNA*) would eventually degrade. The perfect complementary base pairing match between miRNA and target messenger RNA (mRNA) induces target mRNA degradation, while the imperfect match results in the repression of the mRNA translation.

modifications, support abnormal cytosine release, differentiation of cell subsets, B cell hyperactivity and autoantibody production [41].

3.2. Adaptive immunity

The adaptive immune system involved both T and B lymphocytes as major cellular components. One of the RNase III family enzymes, Dicer as mentioned previously is important in the biogenesis of miRNA. In the early stage of T cell development, depletion of Dicer leads to reduction of T cell numbers both in the thymus and peripheral lymphoid organs [42]. Dicer-deficient T helper (Th) cells show aberrant cytokine secretion, such as increased expression of IFN-γ in the absence of exogenous cytokines and blocking antibodies [43]. In early B cell progenitors, depletion of Dicer results in blocking at the pro- to pre-B cell transition since miR-17 mostly target the genes that upregulated in Dicer-deficient pro-B cells [44].

Interleukin (IL)-17 produced by Th17 cells are closely related to miR-326 and miR-155. It is shown that overexpression of miR-326 results in increased number of Th17 cells through targeting Ets-1 in multiple sclerosis patients and severe experimental autoimmune encephalomyelitis (EAE) mice [45]. MiR-155 on the other hand is essential for dendritic cell production of cytokines which induce Th17 cell formation. Mir-155 knockout mice are recognized resistant to EAE [46]. MiR-155 is down-regulated in human monocyte-derived dendritic cells in response to LPS-induced inflammatory processes [47]. MiR-155 expression is necessary for maintaining regulatory T (Treg) cell

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Table 1
Differential expression of miRNAs in autoimmune diseases.

Disease	Sample	miRNA expression			
		Up-regulated		Down-regulated	
SLE	PBMCs	miR-516a-3p	[54]	miR-126	[53]
		miR-525-5p		miR-17-5p	[55]
		miR-629		miR-112	
		miR-21	[55]	miR-141	
		miR-61		miR-184	
		miR-78		miR-196a	
		miR-142-3p		miR-383	
		miR-189		miR-409-3p	
		miR-198		miR-146a	[57]
		miR-298		miR-155	[59]
		miR-299-3p			
		miR-342			
		miR-410	[60]		
	T cells			miR-26a	[61]
	Serum	miR-148-3p	[62]		
		miR-130b-3p	[63]		
	Urinary exosomes	miR-146a	[65]		
APS	Exosome	miR-146a-3p	[66]		
		miR-146a-5p			
		miR-155			
		miR-210			
SS	MSGs	hsa-miR-768-3p	[71]	hsa-miR-574	[71]
		miR-16	[69]		
	SGECs	miR-200b-3p			
	PBMCs	miR-223		miR200b-5p	[69]
		miR-483-5p			
		miR-146a/b	[72]		
		miR-155	[74]	miR-155	[76]
		miR-181a	[77]		
	Monocytes	miR-34b-3p	[78]		
		miR-300			
		miR-609			
		miR-877-3p			
		miR-3162-3p			
		miR-4701-5p			
RA	PBMCs	miR-146a	[80]		
		miR-155			
		miR-301a-3p	[81]		
	Serum	miR-223	[82]	miR-16	[82]
				miR-146a	
				miR-155	
	Synovial tissue	miR-16	[83]	miR-188-5p	[85]
		miR-132			
		miR-146a			
		miR-223			
	FFPE	miR-146a	[84]		
		miR-155			
		miR-223			
	CD4 + T cells	miR-146a	[87]	miR-363	[87]
				miR-498	
	Macrophages	miR-223	[88]	miR-99a	[88]
				miR-100	
				miR-125b	
				miR-199-3p	
				miR-199-5p	
				miR-152	
				miR-214	
SSc	Serum	miR-21	[99–105]	miR-15b	[91–98]
		miR-92a		miR-16	
		miR-133		miR-27a/b	
		miR-142-3p		miR-132	
		miR-200a/b		miR-150	
		miR-590		miR-335	
	Fibroblasts			miR-29a	[106,107]
				miR-135b	[108]
				miR-193b	[109]
MS	PBMCs	miR-21	[111,112]	miR-214	[114]
		miR-146a/b		miR-140-5p	[115]
		miR-155		miR-572	[116]
		miR-326	[113]		
		miR-27a	[114]		
	CSF	miR-150	[117]		
Psoriasis	PBMCs	miR-142-3p	[119]	miR-99a	[119]
		miR-146a		miR-125b	
		miR-155		miR-181a	
		miR-224			
		miR-378			
	Serum	miR-146a	[120]		
	Th17	miR-223	[119]	miR-193b	[119]
	Hair shaft	miR-424	[121]		
	Lesional skin	miR-26b-5p	[122]		

Abbreviations
SLE: systemic lupus erythematosus.
APS: antiphospholipid syndrome.
SS: Sjögren's syndrome.
RA: rheumatoid arthritis.
SSc: systemic sclerosis.
MS: multiple sclerosis.
PBMCs: peripheral blood mononuclear cells.
MSGs: minor salivary glands.
SGECs: salivary gland epithelial cells.
FFPE: formalin-fixed paraffin-embedded synovial tissue.
CSF: cerebral spinal fluid.
Th: T helper cell.

proliferative activity under Foxp3 regulation in controlling the IL-2 signaling pathway by targeting the suppressor of cytokine signaling (SOCS) 1 [48]. Like miR-155, miR-146a is not only relevant to the innate immune system but also critical in the adaptive immune system. Overexpression of miR-146a was found in Treg cells as a response to activation of signal transducer and activator transcription (STAT) 1. The negative regulator of STAT1 phosphorylation downstream of the IFN-γ receptor is SOCS1, which additionally associated with Th1-mediated autoimmunity [49]. In activated B cells, miR-181b results in the down-regulation of activation-induced cytidine deaminase (AID) mRNA and protein levels. By restricting AID activity, miR-181b may prevent B cell malignant transformation [50].

The overexpression of miR-148a results in impaired B cell tolerance, which accelerates the development of autoimmune diseases. Moreover, miR-148a inhibits the expression of the autoimmune suppressor Gadd45α, the tumor suppressor phosphatase and tensin homolog (PTEN) and the pro-apoptotic protein Bim and protects immature B cells from apoptosis induced by engagement of B cell antigen receptor [51].

4. MiRNAs in autoimmune diseases

Alterations in miRNA regulation seem to be highly related to the development of immune dysfunctions and autoimmunity. Recently several studies have focused on the role of miRNAs in autoimmune diseases and different expression profiles have been identified as biomarkers of certain autoimmune conditions, such as SLE, RA and SS. Table 1 summarized the differential expression of miRNAs in autoimmune diseases.

4.1. Systemic lupus erythematosus

SLE is one of the most prevalent systemic autoimmune disorders. SLE has a large spectrum of clinical presentations since the disease can affect multiple organs, including skin, joints, kidneys, lungs, nervous system, and serous membranes. The diversity of its clinical features is matched by the complexity of pathogenic factors including genetic, hormonal, and environmental factors [52].

A recent study demonstrated that blood plasma level of miRNA-126 was significantly lower in SLE patients compared to that in normal controls. In addition, both plasma levels of IFN-α and interferon-inducible gene ISG56 mRNA in peripheral blood mononuclear cells (PBMCs) showed higher levels in SLE patients compared to controls. Based on

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these observations, miRNA-126 may inhibit the production of IFN-α and decrease in its expression level is possibly involved in the pathogenesis of SLE [53].

Zhu et al. reported high expression levels of miRNA-516a-3p, miRNA-629 and miRNA-525-5p in the PBMCs of paediatric SLE (pSLE) patients compared to healthy children. In addition, the increased expression levels of these three miRNAs were positively correlated with the SLEDAI scores and CRP levels. The target genes of these three miRNAs, namely Yinyang1 (YY1), Kruppel-like factor 13 (KLF13) and interferon regulatory factor 5 (IRF5), were found to be important in the pathogenesis of pSLE [54]. Dai et al. indicated 16 miRNAs with altered expression pattern in PBMCs, based on a microarray analysis involving 23 SLE patients from Han population, as following: seven miRNAs are decreased expression in SLE: miR-17-5p, miR-112, miR-141, miR-184, miR-196a, miR-383, and miR-409-3p; the other nine miRNAs are overexpressed in SLE: miR-21, miR-61, miR-78, miR-142-3p, miR-189, miR-198, miR-298, miR-299-3p, and miR-342 [55]. Two years later, they analyzed miRNAs in kidney biopsy samples of class II lupus nephritis (LN) patients, compared to renal tumor patients' kidney resection samples. They reported 66 miRNAs differentially regulated in lupus nephritis patients. Among them, 36 are up-regulated and the rest 30 are down-regulated [56].

The downregulation of miR-146a also contributes to the development of SLE. It was revealed that miR-146a is a negative regulator of type I IFN pathway by targeting IFN regulatory factor 5, STAT 1, IRAK1 and TRAF6 [57]. Two recent studies focused on miR-155; the miR-155 expression level correlated negatively with the expression of CD1d in B cells of SLE mice. Additionally, it was found that lower expression level of CD1d on B cells was decreased by targeting Ets-1 through activation of TLR9. Moreover, in juvenile SLE patients, miR-155 is downregulated in PBMCs compared to that of healthy controls. It was reported that miR-155 expression level was negatively correlated with Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) score [58,59].

It is observed that up-regulation of miR-410 significantly reduced the expression levels of fibrosis factors such as transforming growth factor-β1 (TGF-β1) by inhibiting secretion of IL-6 in the pathogenesis of LN [60]. The epigenetic modulator EZH2 might shift implicating effector in lupus naïve CD4 + T cells and opposes inhibitory TGF-β signaling. The expression level of miR-26a, which is sensitive to glucose availability and targets EZH2, correlated negatively with SLEDAI [61].

A current study indicated that miR-148a-3p expression level was significantly higher in blood serum and glomerular cells in SLE with active LN. Up-regulation of miR-148a-3p accelerated glomerular cell proliferation and proliferating cell nuclear antigen (PCNA) expression, consequently reducing the PTEN expression level [62]. The significant overexpression of miR-130b-3p was demonstrated in serum of SLE patients with early stage LN, compared with that measured in healthy controls. Serum miR-130b-3p did not affect SLE disease activity (SLEDAI, ds-DNA, and complements levels) but correlated with renal damage since the expression of serum miR-130b-3p correlated positively with 24-h proteinuria and chronicity index (histological chronicity index and glomerular sclerosis) [63]. On the other hand, miR-29c expression in urinary exosomes showed a strong negative correlation with the chronicity but not with renal function (eGFR and creatinine levels). Urinary exosomes are micro-vesicles released by the epithelial cell facing the urinary space and proposed a novel and ideal source of markers for evaluating stage of LN [64]. Furthermore, expressions of several miRNAs were elevated in the urinary exosome fraction compared to the cell-free and exosome-depleted supernatant fraction, especially with LN. Among the exosomal miRNAs, miR-146a was the most over-expressed in SLE patients with active LN compared to the control group or to the SLE patients in the absence of LN [65].

Circulating antiphospholipid antibodies (aPLs) increase the risk of pregnancy complications, which leads to an autoimmune disorder named antiphospholipid syndrome (APS). APS patients with adverse pregnancy outcomes showed significantly higher levels of circulating exosomal-associated miR-146a-3p compared to healthy pregnant controls. The specific aPL significantly induced trophoblasts to express higher level of miR-146a-5p, miR-146a-3p, miR-155 and miR-210. Except miR-155, the other miRNAs were inhibited by the TLR4 antagonist. The suppression of miR-146a-3p significantly reduced aPL-induced trophoblast IL-8 secretion regulated by the TLR8 [66].

4.2. Primary Sjögren's syndrome

Primary SS is a slowly progressive systemic autoimmune inflammatory disease that primarily affects middle-aged women (female to male ratio: 9:1), although it may be found in all ages including childhood. The target organs are primarily exocrine glands, such as salivary and lachrymal glands. Therefore, patients show typically symptoms of dry mouth and dry eyes [67]. Besides the pathognomonic glandular symptoms (GS), other systemic symptoms, denoted as extraglandular manifestations (EGMs) (e.g. polyarthritis, myositis, vasculitis, polyneuropathy etc.) can also develop during the disease course in approximately one third of the patients [68].

The increase of Ro/SSA and La/SSB autoantigens is a common feature in SS patients. The miRNAs which are suspected to target Ro/SSA and La/SSB mRNAs in primary SS are as follows: let-7b, miR-16, miR-181a, miR-200b-3p, miR-200b-5p, miR-223 and miR483-5p. The overexpression of miR-16 in minor salivary glands (MSGs), miR-200b-3p in salivary gland epithelial cells (SGECs) and miR-223 together with miR-483-5p in PBMCs of 29 SS patients compared to 24 sicca-complaining controls has been shown previously. Significant lower-expression of miR200b-5p levels was reported in SS patients with mucosa-associated lymphoid tissue (MALT) lymphoma compared to primary SS patients [69]. Another study demonstrated the positive correlation between the expression levels of La/SSB and the Dicer enzyme in connection with cancer prognosis. La/SSB promotes global microRNA expression and identifies stem-loop [70]. Alevizos et al. generated microRNA microarray profiles from the minor salivary glands of patients with SS who had low-grade or high-grade inflammation and impaired or normal saliva production, and compared the results with that observed in healthy control subjects. They found hsa-miR-768-3p over-expression, while hsa-miR-574 was underexpressed in patients' biopsies; additionally, their inverse correlations to focus scores were also demonstrated [71]. Previously, our workgroup not only confirmed the over-expression of miR-146a/b in PBMCs of SS but also demonstrated the unanticipated over-expression of its functionally targeted gene, TRAF 6. Furthermore, we also reported decreased gene expression of IRAK 1 [72]. The over-expression of TRAF6 is surprising since miR-146a could inhibit the expression of TRAF6 [73]. Recently, enhanced expression of miRNA-155 was reported in untreated Sjögren's syndrome [74]. Of note, SS patients treated with immunosuppressants also showed the over expression of miR-155. On the contrary, in Asian population the relative expression of miR-155 was lower in PBMCs of SS patients not receiving any immunosuppressive treatment than the controls, which may emphasize the importance of the diverse genetic background of different ethnicities [75,76]. A recent study demonstrated the over-expression of miR-181a in the PBMCs of pSS patients, which was associated with the up-regulation of several virus-derived miRNAs, suggesting that viral infection of PBMC plays a role in the disease [77].

Up-regulated expression of miR-34b-3p, miR-4701-5p, miR-609, miR-300, miR-3162-3p, and miR-877-3p in SS monocytes compared to controls may relate with opposing of TGF-β signaling pathway and TLR/NF-κB pathways induced pro-inflammatory IL-12 secretion [78].

4.3. Rheumatoid arthritis

RA is a frequent autoimmune disorder with prevalence rates approximately 1% of the adults worldwide. The disease primarily affects the synovial joints, and the chronic inflammatory process consequently causes the destruction of the articular tissue [79].

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Associations between the alterations in miRNA expressions and the pathomechanisms of the disease have been shown previously. Elevated expression of miR-146a and miR-155 was determined both in whole blood samples and PBMCs of RA in Canadian cohort in comparison with healthy individuals [80]. The expression of the transcription factors (RORγt and STAT3) of Th17 cells was significantly increased in the PBMCs of RA patients while miR-301a-3p was also found overexpressed. Levels of miR-301a-3p showed positive correlation with the frequency of Th17 cells in RA patients [81]. MiR-146a, miR-155 and miR-16 were found to have lower expression levels in the serum of early stage of RA patients who were prior to and after 3 and 12 months of antirheumatic drugs therapy compared to established RA. Based on a recent observation, miR-223 may be a potential marker of disease activity since decreased serum level of miR-223 was found after therapy in early RA [82].

MiR-16, miR-132, miR-146a, and miR-223 were found to be overexpressed in synovial fluid and blood plasma of patients compared to healthy controls. No correlation was identified between plasma and synovial fluid miRNAs although concentrations of miRNAs in synovial fluid were significantly lower compared to that of plasma levels [83]. A very recent study showed altered expression levels of certain miRNAs in formalin-fixed paraffin-embedded synovial tissue (FFPE) samples of patients with RA compared to osteoarthritis (OA) patients. It was reported that miR-146a, miR-155, and miR-223 were upregulated significantly in FFPE samples of established RA patients [84].

It was also shown that miR-188-5p is downregulated in synovial tissue samples of RA patients as well as in RA synovial fibroblasts (RASF). Moreover, it was revealed, that miR-188-5p is directly and indirectly regulating the expression of genes confirmed by gene expression profiling in RASF, including hyaluronan binding protein KIAA1199 as well as collagens COL1A1 and COL12A1, which may correlate with extracellular matrix formation and destruction in RA [85].

MiR-573 might be a negative regulator in RA since miR-573 could suppress the activation of mitogen-activated protein kinase (MAPK) which is regarded as one of the potential targets for RA treatment [86].

Regarding CD4+ T cells of RA patients, miRNA expression analysis indicated significant upregulation of miR-146a expression, while miR-363 and miR-498 were downregulated [87].

The miRNA expression in macrophages from patients with active RA and OA was recently determined. Seven miRs, namely miR-99a, miR-100, miR-125b, miR-199-3p, miR-199-5p, miR-152 and miR-214 were downregulated and only miR-223 was upregulated in macrophages in RA, compared to the results from OA samples. It was also implied that high miR-223 levels functionally impair the AHR (aryl hydrocarbon receptor)/ARNT (AHR nuclear translocator) pathway in myeloid cells by reducing ARNT protein levels. The AHR activation may be linked to the pathogenesis of RA, since AHR agonists inhibit pro-inflammatory cytokine expression in macrophages [88].

A recent study investigated single nucleotide polymorphisms (SNP) rs22928323 of miR-149 in 200 RA patients and 120 healthy controls. Rs22928323 showed correlation with RA development but was not associated with further clinical characteristics [89].

4.4. Systemic sclerosis

SSc is characterized by accelerated fibrosis and tissue damages in the skin and visceral organs such as heart, lungs and kidneys. SSc can be classified into two sub-groups based on the extent of skin thickening: limited SSc and diffuse SSc. Patients with the limited form are at lower risk of having visceral involvement, while the diffuse form involves several systems of internal organs [90].

Different study groups reported how miRNAs regulate fibrogenesis. The miR-15b, miR-16, miR-27a, miR-27b, miR-132, miR-150, and miR-335 seem to play an important role in the induction of myofibroblast proliferation and resistance to apoptosis [91–98]. On the contrary, miR-21, miR-92a, miR-133, miR-142-3p, miR-200a/b, and miR-590 have been shown to suppress fibrotic processes [99–105].

Regarding other miRNAs, miR-29a was considered as the most direct regulator of extracellular matrix (ECM) synthesis. It targets the gene TAB1 and may lead to apoptosis of the dermal fibroblasts resulting to lower TIMP-1 production and promote collagen degradation by increasing MMP-1 production, suggesting that miR-29a may be a potential therapeutic target for SSc [106]. The restoration of miR-29a decreased TNF-α production in dermal fibroblasts of SSc patients. Moreover, Bcl-2 expression was upregulated in SSc fibroblasts and the ratio of Bax:Bcl-2 in fibroblasts was significantly lower compared to normal controls. However, miR-29a disrupted the expression profiling of Bcl-2 family proteins (Bax, Bcl-2 and Bcl-XL), which proved that miR-29a is an anti-fibrotic factor induce apoptosis and an attenuator cause ECM production in SSc fibroblasts [107].

Additionally, miR-135b expression is significantly lower both in serum and isolated CD14+ monocytes from patients compared to controls. T cell-derived IL-13 increased collagen expression in dermal fibroblasts which was dependent on STAT6 and miR-135b. Besides, miR-135b is repressed by methylation and could be mediated by the repressive protein methyl cap binding protein 2 (MeCP2), which is significantly enhanced in SSc dermal fibroblasts compared to controls [108].

Iwamoto et al. reported the downregulation of miR-193b in SSc fibroblasts and skin sections. Knockdown of miR-193b induced the expression of mRNA and urokinase-type plasminogen activator (uPA) enzyme, which was strongly expressed in vascular smooth muscle cells in SSc skin section and contributed to the proliferative vasculopathy with intimal hyperplasia characteristic for SSc [109].

4.5. Multiple sclerosis

Multiple sclerosis is an autoimmune neurological disease which affects the brain and the spinal cord thus leading to the main triad symptoms of inflammation, demyelination and gliosis. The damage of the protective covering of the myelin sheath surrounding the nerve cells result in single or multiple symptoms including motoric, speech, swallowing, and visual disabilities and other neuronal problems [110].

MiR expression profile analysis indicated significant overexpression of miR-21, miR-146a, miR-146b and miR-155 in PBMCs of relapsing remitting MS patients compared to controls [111,112]. MiR-326 promotes differentiation by targeting Ets-1, furthermore, its overexpression leads to Th17 cell proliferation and disease aggravation in experimental autoimmune encephalomyelitis [113]. Upregulation of miR-27a was observed in relapsing phase of MS compared to remitting phase and healthy controls; on the contrary, miR-214 was underexpressed in relapsing phase of MS, which implied that miR-27a may inhibit Th17 cell differentiation, while miR-214 may promote Th17 cell differentiation [114].

The expression of miR-140-5p was found to be significantly decreased in the PBMCs of MS patients compared to those in controls, and miR-140-5p level was inversely correlated with disease severity. Transfection of synthetic miR-140-5p in PBMCs inhibited activation of STAT1 and consequently suppressed the encephalitogenic Th1 differentiation, which suggests that miR-140-5p may be a novel marker involved in the pathogenesis of MS [115].

Another group recently reported significantly lower expression of miR-572 in overall MS patients, compared to healthy controls. MiR-572 was found to be significantly upregulated in secondary progressive and relapsing remitting MS, while it was downregulated in primary progressive MS. Consequently, with the different potential, this miRNA could be regarded as a non-invasive biomarker for remyelination [116].

The expression level of miR-150 was elevated in cerebral spinal fluid (CSF) from patients with clinically isolated syndrome (CIS) who convert to MS later, compared to those CIS who did not convert during follow-up (median period of 52 months). The miR-150 may be regarded as a marker of CNS inflammation, since higher levels of miR-150 correlate

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with higher levels of CSF biomarkers, involving C-X-C motif chemokine 13 (CXCL13), matrix metallopeptidase 9 (MMP-9) and osteopontin. Additionally, the level of miR-150 in CSF decreased after treating with natalizumab for one year and remains unchanged with fingolimod, while level of miR-150 in plasma increased after the treatment with natalizumab and decreased after fingolimod therapy [117].

4.6. Psoriasis

Psoriasis is a chronic and frequently relapsing inflammatory skin disease characterized by pathologic features such as accelerated epidermopoiesis, marked hyperkeratosis with parakeratosis, vascular dilatation, and inflammatory cell infiltration. The most common form of the disorder is the chronic plaque psoriasis with rounded erythematous, dry, scaling patches. The lesions have a predilection site as nails, scalp, genitalia, extensor surfaces, and the lumbosacral region [118].

Recently, a study group discovered 24 dysregulated miRNAs in the epidermis of psoriatic skin and 37 dysregulated miRNAs in the dermal inflammatory infiltrates of patients. Among those, miR-99a, miR-125b and miR-181a were significantly lower expressed in PBMCs while miR-142-3p, miR-146a, miR-155, miR-224 and miR-378 were upregulated. Moreover, miR-193b was downregulated and miR-223 was upregulated in Th17 cells, while miR-125b was downregulated in T regulatory cells [119]. MiR-146a level was up-regulated in blood samples from patients of psoriasis in comparison with healthy controls, but no significant positive relation was revealed with PASI scores in patients. However after 12 weeks of treatment with Narrow-Band Ultraviolet B phototherapy or treatment with methotrexate, expression of miR-146a decreased dramatically, which suggests that miR-146a may be useful in evaluating and screening the effect of treatment of psoriasis objectively [120].

Even though miR-424 levels were not correlated with disease activity markers, such as PASI (psoriasis area and severity index), hair shaft; miR-424 levels were significantly upregulated in psoriasis patients compared with normal controls and those with atopic dermatitis [121].

A recent study reported increased level of miR-26b-5p in subcutaneous adipose tissue under lesional psoriasis skin compared to nonlesional psoriatic skin. miR-26b-5p down-regulates neutral cholesterol ester hydrolase 1 enzyme, which is essential for cholesterol efflux, in monocytes/macrophages, adipocytes, vascular endothelial cells and fibroblasts [122].

Additionally, the G allele of SNP rs2910164 in miR-146a regarded as a risk factor, which would impair its suppression on the proliferation of keratinocytes through the decreased inhibition of the target gene [123].

5. Conclusions and future perspectives

The discovery of miRNAs and the recognition of their critical role in modulating gene expression changed the way we think about genetic control. The intensive research over the last decade shed light on multiple pathways and modes how miRNAs regulate cell development and differentiation. The central role of miRNAs in modulating immune system responses was also recognized, although, there are numerous questions about miRNAs, yet to be answered.

In the last years much attention was drawn to the function of miRNAs in autoimmunity. Changes in the expression levels of certain miRNAs in the circulation or in different cells and tissues are characteristics for various autoimmune conditions and presumably contribute to disease development. Consequently, some of these molecules may be regarded as novel and attractive biomarkers specific for different autoimmune disorders. However, functional experimental studies are required to verify and establish the causal association between the aberrantly expressed miRNAs and the development of disease. Additionally, the mechanisms underlying the aberrant expression of miRNAs, as well as the influence of other factors that regulate miRNAs, also remained to be investigated.

Genome-wide surveys identified many single nucleotide polymorphisms (SNPs) in the predicted miRNA target sites, as well as in miRNAs themselves. In some instances, SNPs have been shown to alter miRNA function, thus possibly contributing to disease development. The better understanding of the immune regulatory mechanisms of miRNAs by pathway-based exploratory analyses and the mapping and characterization of miRNA SNPs may help not only to elucidate the pathogenesis of autoimmune conditions but also can lead to the development of complex therapeutic approaches in patients with immunological disorders.

Take-home messages

- Alterations of miRNAs expression are involved in the development of autoimmune conditions.
- Certain miRNAs could be regarded as novel and specific biomarkers for different autoimmune diseases.
- Exploration of miRNA target genes will define their role in autoimmunity and reveal novel targets and therapeutic approaches.

Conflict of interest

No disclosure to report.

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