Review Article

Aberrant non-coding RNA expression profiles as biomarker/bio-signature in autoimmune and inflammatory rheumatic diseases

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Abstract: Non-coding RNAs (ncRNA) are functional RNA molecules transcribed from DNA but not translated into protein. The major function of ncRNA is to modulate messenger RNA (mRNA) expression. Conventionally, these ncRNAs are categorized into long non-coding RNAs (lncRNAs, longer than 200 nucleotides) and small non-coding RNAs (sncRNAs, shorter than 200 nucleotides). microRNAs (miRNAs), a member of sncRNA with 20–24 nucleotides, have been demonstrated to be involved in the development of innate and adaptive immune systems. As a result, aberrant expression of miRNAs may elicit autoimmune and inflammatory reactions. Although many different biomarkers in the cell, serum or body fluid have been reported, the ideal biomarkers or bio-signatures for the diagnosis, disease activity evaluation, therapeutic monitoring, or outcome prediction of various diseases have still not been found. Recently high-throughput "omics" assay including proteomics, transcriptomics or metabolomics, and bioinformatic analysis have revealed that thousands of ncRNAs can potentially become biomarkers/bio-signatures for autoimmune-related diseases. In this mini-review, we'll try to identify the useful miRNA biomarkers/bio-signatures from the literature including ours, to clarify the potential pathogenetic/pathological processes mediated by these miRNAs and to disclose their future prospects.

Keywords: Non-coding RNA (ncRNA); microRNA (miRNA); long non-coding RNA (lncRNAs); small non-coding RNA (sncRNAs); biomarker; bio-signature; autoimmune diseases; inflammatory rheumatic disease

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Introduction

Autoimmune status is elicited by multi-etiologic factors (1,2) that may include genetic predisposition (3-5), epigenetic dysregulation (5-7), gender bias and hormone imbalance (8-11), environmental stimulation (12,13), host-microbiota dysbiosis (14-18) and triggering from stochastic events (1,2,19). The intricate interactions among these etiologic factors lead to a state of "loss of self-tolerance" in susceptible individuals. Furthermore, a self-sustaining mechanism operates via autoimmune-mediated local inflammation, tissue destruction, and autoantigen epitope spreading elicited by sophisticated interactions among pathogenic autoantibodies, autoreactive T cells and pro-inflammatory cytokines (1-21). A scheme demonstrating the involvement of these factors in the pathogenesis of autoimmunity is shown in *Figure 1*.

In the respect of epigenetic modulation of immunity and autoimmunity (22-24), there are many genetic on/off regulatory modes such as methylation/acetylation of CpG islets in cytokine genes (7,25-27), histone modification by

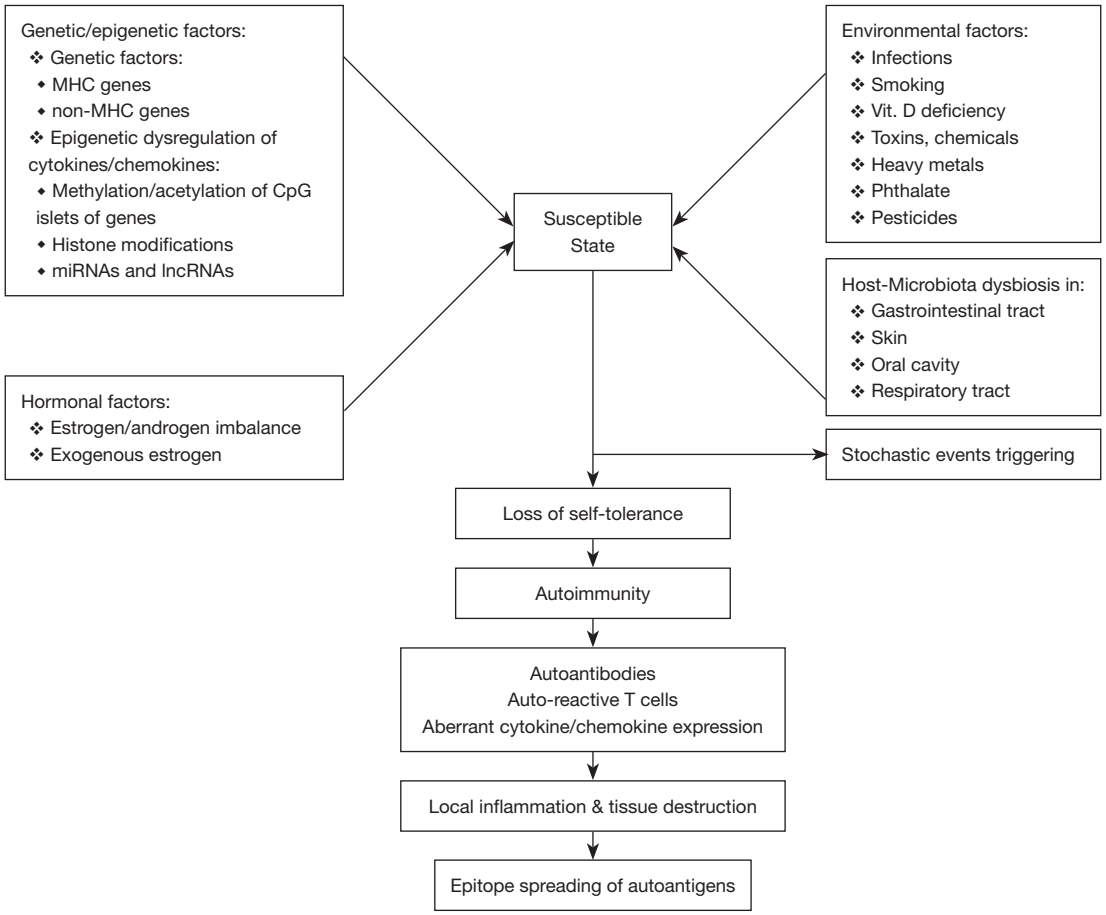

Figure 1 Multiple etiologic factors implicated in the initiation and then induction of a self-sustaining mechanism for the chronicity of autoimmune diseases.

histone deacetylase/histone acetyltransferase (22,23,28-30) and post-transcriptional modification of messenger RNAs (mRNAs) by non-coding RNA (ncRNA) (31-36). On the other hand, high-throughput detection technology of transcriptomes and bioinformatic analysis have found the presence of thousands ncRNAs in the cytoplasm and body fluids in charge of regulating mRNA expression. In conjunction with proteomic (37-39) and metabolomic profiling technologies (40-42), many investigations have tried to find the useful biomarkers/bio-signatures for diagnosis, disease activity & therapeutic monitoring as well as outcome prediction of autoimmune and inflammatory rheumatic diseases. In fact, the "omics" studies have demonstrated many biomarkers or bio-signatures in the literature (43-46). In addition, these array profiles can concomitantly elucidate the potential molecular pathways in the development of autoimmune and inflammatory rheumatic diseases (44). However, either biomarkers or bio-signatures must fulfill the criteria (47,48) as shown in *Table 1* to become useful monitoring parameters in the clinical practice.

The ncRNAs are conventionally classified into two categories, long non-coding RNAs (lncRNAs) and small non-coding RNAs (sncRNAs), cutoff at the nucleotide (nt) or base pair (bp) number of 200. The RNAs with molecular size larger than 200 nt are classified as lncRNAs whereas those with molecular size shorter than 200 nt belong to the sncRNA category. lncRNAs can be further divided into 7 subtypes according to their lineage-specific effects on mRNA regulation for the innate and adaptive immune homeostasis (34,35) (*Figure 2*). In contrast, sncRNAs are divided into at least nine subtypes according to the size, argonaute (Ago) protein association and their major localization (*Table 2*) (36,49). Single nucleotide polymorphisms (SNP) in human genes disturb genome stability (49) and induce inflammatory rheumatic disorders (35). In this review, we will discuss in detail

Table 1 Definition, classification and ideal criteria for a useful biomarker or bio-signature in clinical practice

Definition of biomarker by the Biomarker Definition Working Group
"A characteristic that is objectively measured and evaluated as an indicator or normal biological processes, pathological processes, or pharmacological responses to a therapeutic intervention"
Definition of bio-signature
The obtained data from high-throughput "omics" together define a biomarker
A major issue is the low reproducibility and limited biological interpretability of the candidate biomarker signature
The detected molecular species include genes and their transcripts, proteins, metabolites and non-coding regulatory RNAs
Types of biomarkers
Predictive (risk) biomarkers
Diagnostic biomarkers
Disease activity monitoring biomarker
Prognostic biomarkers
Ideal criteria for a biomarker
A disease-causing molecule with high sensitivity and specificity
General usability and high reproducibility
Low cost
Logistic interpretability

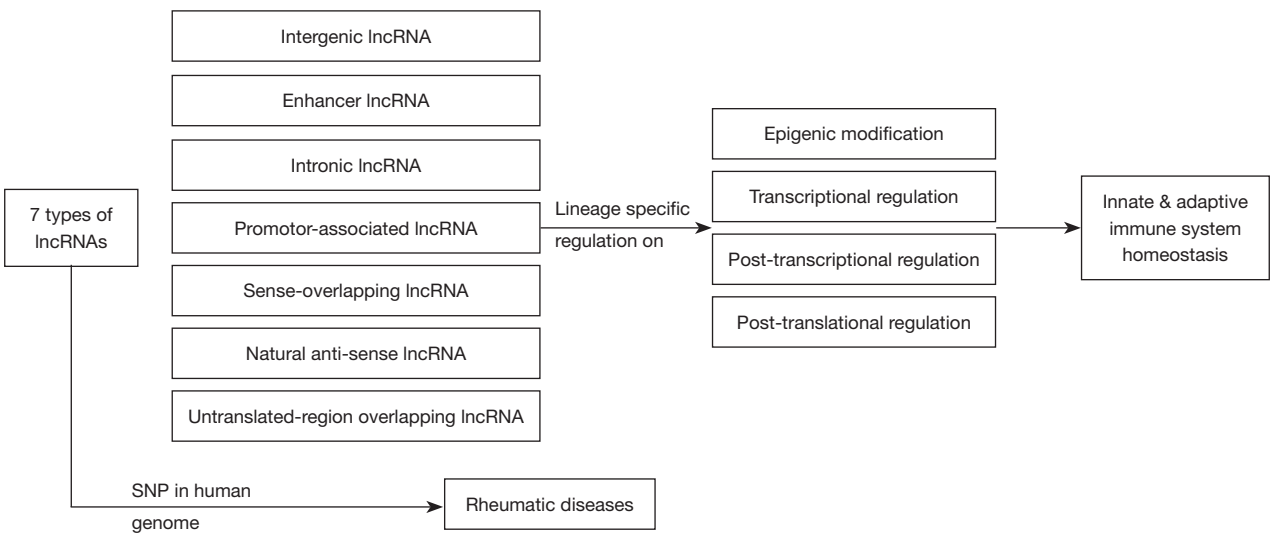

Figure 2 Modulation of innate and adaptive immune homeostasis by seven types of long non-coding RNAs (lncRNAs) via lineage-specific manner. Single nucleotide polymorphisms (SNPs) in human genome induce inflammatory rheumatic diseases.

the biological functions of ncRNAs in the development of immune system and their aberrant expression profiles resulting in the pathogenetic and pathological processes of various autoimmune-related diseases.

Biology of ncRNAs

RNAs are traditionally regarded as informational intermediate between a DNA (gene) and its encoding product protein.

Table 2 Classification of non-coding RNAs (ncRNAs) implicated in regulating gene expression

Nomenclature of ncRNA	Size (bp)	Ago protein association	Localization
Long non-coding RNAs (lncRNA)	>200	N/A	Nucleus
Small non-coding RNAs (sncRNA)	<200	Ago	Nucleus, cytoplasm
Small interference RNAs (siRNA) & endogenous siRNA	20–24	Ago	Nucleus
Guide RNAs (gRNA)	50–70	N/A	Nucleus
PIWI interacting RNAs (piRNA)	23–31	PIWI	Nucleus, cytoplasm
Promotor association RNAs (pRNA)			Nucleus
Small nucleolar RNAs (snoRNA) & sno-derived RNAs	<200		Nucleolus
MicroRNAs (miRNA)	20–24	Ago	Cytoplasm
Double-stranded break-induced small RNAs (diRNA)	20–24	Ago	Nucleus
Circular RNAs (cirRNA)			Nucleus
Exosomal miRNAs (exo-miR)	20–24	Ago	Plasma, body fluids, extracellular space

Ago, argonaute; PIWI, P-element-induced wimpy testis.

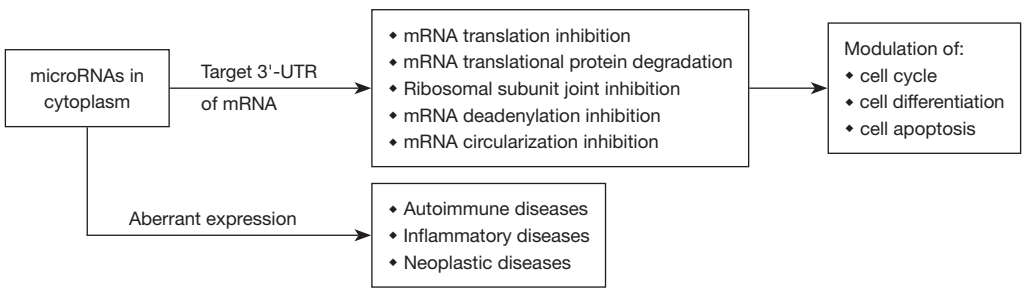

Figure 3 Intracellular miRNAs target mRNAs in the site of 3'-UTR by different mechanisms to modulate cell physiology including cell cycle, cell differentiation and cell apoptosis. Aberrant miRNA expression induces autoimmune, inflammatory rheumatic, and neoplastic diseases.

In fact, around 70–85% of the human genome are actively transcribed into RNAs. However, only 2% are transcribed into protein-coding mRNAs. This fact implies that the number of ncRNAs is much higher than that of the protein coding genes (36,50). lncRNAs (>200 bp) are lineage-specific regulators of mRNAs, which can modulate innate and adaptive immune homeostasis by epigenetic, transcriptional, post-transcriptional and post-translational regulations (*Figure 2*). In contrast, miRNA (20–24 bp in length) can target several transcripts rather than a single specific transcript of genes in the site of 3'-UTR (51). Up to the present, more than 9,000 miRNAs have been identified to carry out various enhancing or suppressing functions on mRNA (52,53). These modulatory functions of miRNAs are obviously crucial in physiological and pathological conditions (36). *Figure 3* demonstrates the modulation of miRNAs on the cell cycle, cell differentiation and cell apoptosis by way of different inhibitory activities on mRNA. Aberrant expression of ncRNAs may induce a number of autoimmune, inflammatory rheumatic, and neoplastic diseases. Indeed, an autoimmune disease is mainly characterized by the presence of autoantibodies and autoreactive T lymphocytes. Examples include systemic lupus erythematosus (SLE) or type 1 diabetes mellitus (T1DM). On the other hand, an inflammatory rheumatic disease is characterized mainly by inflammation rather than a presence of obvious autoantibodies or autoreactive cells. These include seronegative spondylarthropathy or

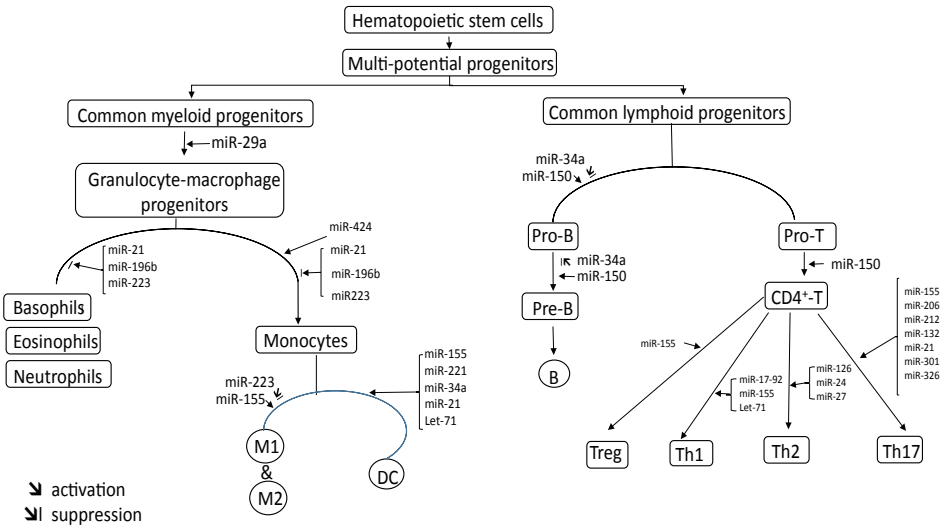

Figure 4 Intracellular miRNAs regulate differentiation of hematopoietic stem cells and multi-potential progenitor cells into different mature innate and adaptive immune cell subpopulations [adapted with permission from Montagner *et al.* (31), and Mehta *et al.* (33)].

inflammatory bowel disease (IBDs).

miRNAs are crucial regulators in the development of hematopoietic stem cells and immune systems

It has been demonstrated that the differentiation and homeostasis of the hematopoietic system require complex interconnected regulatory networks to distinguish the different blood cell lineages. The major immune system includes innate (monocytes, macrophages, dendritic cells, natural killers and leukocytes) and adaptive (B cells, T cells and a variety of T cell subsets) immune cells, which are originated from hematopoietic stem cells. Among the regulatory molecules in hematopoiesis, miRNAs play a pivotal role in the fine-tuning of differentiation in the system (31,33,54,55). Knockout or silencing of certain miRNA machinery results in severe compromise of the immune system. The involvement of miRNAs in immune system development is depicted in *Figure 4*. The aberrant expression of miRNAs in hematopoiesis can undoubtedly elicit autoimmune, inflammatory rheumatic and neoplastic diseases (56-58).

Aberrant miRNA expression profiles of T cells become bio-signature of the pathogenesis and disease activity in patients with SLE

Many investigators have tried to detect and confirm the miRNA expression profiles in the immune cells, plasma or other body fluids by using miRNA extraction kits, miRNA reverse transcription kits and miRNA microarray for early detection, and real-time quantitative polymerase chain reaction (PCR) for confirmation. However, the data of individual T cell miRNA expression profiles in the literature for SLE risk or pathogenesis are quite variable (44,59-67). Lu *et al.* (62,65) have found decreased miR-145, increased miR-224, and aberrant Ca^{2+} influx-regulated ncRNAs play roles in lupus pathogenesis. Later, they have extensively reviewed the literature and concluded that a number of elevated miRNAs could potentially become bio-signatures for immunopathogenesis of SLE (68). These bio-signatures include elevation of miR-17–92 cluster, miR-21, miR-296, miR-126, miR-148a, miR-224, miR-524-5p, and suppression of miR-31, miR-125a, miR-125b, miR-142-3p, miR-142-5p and miR-146a. In addition, these bio-signatures are found intriguingly correlated with T cell subset alteration, aberrant cytokine/chemokine release, altered gene transcription and immune cell signaling abnormalities in SLE (68). Besides, urinary exosomal miRNA profiling was also investigated as bio-signatures for lupus nephritis (69-71). These include increased miR-125a, miR-146, miR-150 and miR-155, and decreased miR-141, miR-192 and miR-200a. For exploring the miRNA expression profiles in the damaged target tissues, Cardenas-Gonzalez *et al.* (72) directly identified, confirmed and explicated miR-30c-5p, miR-1273e and miR-3201 in the

renal tissue of patients with lupus nephritis. This cause-effect relationship investigation of the damaged tissue is direct and more reliable than the conventional correlation analysis (73,74).

Abnormal miRNA expression profile reflects the pathogenesis, helps diagnosis and indicates therapeutic prognosis in patients with rheumatoid arthritis (RA)

Similar to the miRNA study in SLE, different investigators have demonstrated variable miRNA expression profiles in patients with RA, reflecting its pathogenesis and helping therapeutic monitoring (74-82). The abnormal miRNA expression in RA includes increase in miR-15a, miR-16, miR-21, miR-25, miR-124a, miR-146a, miR-155, miR-203, miR-223 and miR-346, and decrease in miR-140-3p and miR-140-5p. Some unique therapeutic strategy, using miRNA antagonist or agonist, can ameliorate the inflammation in RA (83-85). Shi et al (83) found miR-27a could inhibit migration and invasion of fibroblast-like synoviocytes by targeting follistatin-like protein 1 in RA (83). Sharma *et al.* (79) demonstrated key components of cytokine signaling and inflammation which is regulated by miRNA. Furthermore, Lai *et al.* (85) have found that anti-citrullinated protein antibodies can suppress let-7a expression and facilitate inflammatory responses in patients with RA. Lai *et al.* (68) have tried to correlate the miRNA expression profile with rheumatoid pathogenesis by meta-analysis. They noted a decrease in miR-21 expression, enhanced STAT3 but suppressed STAT5, which upsurge T-helper 17 (Th17)/regulatory T cell (Treg) ratio. Increased expression of miR-23 may diminish IL-10 production, leading to imbalance between pro-inflammatory and anti-inflammatory cytokine production. Furthermore, increased LOC100506036 (a kind of lncRNAs) expression enhanced transcription factors such as nuclear factor of activated T cell (NFAT) and Smith deoxyribonuclease protein (SMDP), which eventually activates T cells.

Aberrant miRNA transcription in other systemic and organ-specific autoimmune diseases

Primary Sjögren's syndrome (pSS)

pSS is featured by systemic autoimmunity and chronic inflammation with dysfunction of exocrine glands. Twenty-five miRNAs including miR-146a, miR-16 and miR-21 were found over-expressed in both pSS and SLE patients. On the contrary, down-regulation of miR-150-5p, which is novel and unique, has been found in pSS (86,87). Wang-Renault *et al.* (88) further demonstrated that hsa-miR-30b-5p, hsa-miR-222-3p, hsa-miR-26a-5p, hsa-miR-30b-5p and hsa-miR-19b-3p were differentially expressed in B cells of pSS patients. Functional studies revealed that inhibition of hsa-miR-30b-5p by miRNA antagonist enhanced the expression of B cell activating factor of TNFR superfamily (BAFF) in B cells originated from pSS patients. These miRNA expression profiles can become the pathogenetic bio-signatures of pSS.

Anti-phospholipid syndrome (APS)

APS is diagnosed in autoimmune patients with a persistent presence of anti-phospholipid antibodies against mainly β2-glycoprotein I and different phospholipids including phosphatidylserine, phosphatidylcholine, and phosphatidylethanolamine, which manifests as arterial or venous thrombosis as well as pregnancy morbidity. The miRNA expression profiles relevant to APS were miR-19b and miR-20a that were implicated in the signaling pathways of TGF-β and vascular endothelial cell growth factor (VEGF), hypoxia and angiogenesis (89,90). These miRNAs can potentially be used as pathogenetic bio-signatures for primary APS. However, no investigation has been reported for the specific miRNA expression profile relevant to obstetric APS patients.

Systemic sclerosis (SSc)

SSc is characterized by Raynaud's phenomenon in the early stage which eventually leads to generalized fibrosis of the skin and internal organs due to overproduction of TGF-β. Steen *et al.* (91) evaluated the cell-free miRNA expression profile in plasma from SSc patients. They found that miR-16, miR-223, and miR-638 were elevated and relevant to the TGF-β signaling and tissue fibrosis. In addition, miR-638 was found weakly correlated with the serum titer of anti-Scl-70 antibody. The authors also noted the differential expression of miR-142-3p, miR-150, miR-150, and miR-638 among SSc and SLE patients.

T1DM

T1DM is an organ-specific autoimmune disease

characterized by selective destruction of pancreatic β-cells driven by the immune dysfunction. The role of miRNAs in T1DM has been explored by experiments using known pancreatic islets as cell-based disease models (92). Indeed, it was found that virus-induced miRNA dysregulation seemed implicated in the immune-mediated β-cell destruction. Zheng *et al.* (93) have reviewed recent data by focusing on the miRNAs involved in immune homeostasis and regulation of the β-cell function in T1DM. Assmann *et al.* (94) have also extensively reviewed the literature and found the results were inconclusive with only few miRNAs consistently dysregulated among these studies. It is concluded that 11 miRNAs including miR-21-5p, miR-24-3p, miR-100-5p, miR-146-5p, miR-148a-3p, miR-150-5p, miR-181a-5p, miR-210-5p, miR-342-3p, miR-375 and miR-1275 may potentially become the circulating pathogenetic bio-signatures for T1DM.

Myasthenia gravis (MG)

MG is characterized by the progressive muscle weakness and the presence of serum autoantibodies specific for either acetylcholine receptor ($AChR^+$) or muscle-specific tyrosine kinase ($MuSK^+$). These two autoantibodies are antagonistic antibodies that can block the neuronal transmission or muscle contraction. However, they do not reflect exactly the disease progression. Punga *et al.* (95) demonstrated that plasma levels of miR-150-5p and miR-21-5p were elevated in $AchR^+$ MG patients who were immunosuppressed and improved clinically after thymoma resection. On the other hand, up-regulation of let-7 family has been found in $MuSK^+$ MG patients. These circulating miRNAs can be considered as useful biomarkers for diagnoses, disease activity evaluation, therapeutic monitoring and foreseeing prognosis in MG patients.

Graves' disease (GD)

GD is an archetype of organ-specific autoimmune disease characterized by aberrant Treg function and subsequent production of anti-thyroid stimulatory hormone receptor (TSHR) antibodies (96). The anti-TSHR antibodies are agonistic antibodies that can facilitate the synthesis and secretion of thyroxine. Hiratsuka *et al.* (97) demonstrated that increased let-78-3p and miR-339-5p as well as decreased miR-23b-5p and miR-92a-39 in intractable GD can lead to IL-1β and TNF-α production and suppression of the Treg function.

Multiple sclerosis (MS)

MS is a life-long organ-specific autoimmune inflammatory disorder of central nervous system featured by immune cell infiltration, degeneration of axons and neurons, local demyelination/remyelination and astrogliosis. Kacperska *et al.* (98) have reviewed the literature and concluded that circulating miR-146 and miR-153 are correlated with high sustenance, tissue specificity and TLR-4 activation (indicating inflammation) in MS patients.

Table 3 summarizes various ncRNA-mediated pathological processes in different autoimmune diseases.

Aberrant miRNA expression profiles in inflammatory rheumatic diseases

Ankylosing spondylitis (AS)

AS is a common and genetically based heterozygous inflammatory rheumatic disease featured by inflammation of the axial and peripheral joints, new bone formation, and spinal ankylosis. High levels of miR-146a-5p, miR-151a-3p, miR-125a-5p and miR-22-3p expression as well as low levels of miR-150-5p, and miR-451a have been shown in AS. Furthermore, miR-146a-5p, miR-125a-5p, miR-151a-3p, miR-22-3p and miR-451a are more likely to be associated with AS than to be associated with psoriatic arthritis. On the other hand, miR-146a-5p, miR-125a-5p and miR-22-3p expression is increased in active versus inactive status of AS. miR-125a-5p, miR-151a-3p, miR-150-5p and miR-451a are relevant to the development of syndesmophytes in AS (99-101).

Psoriasis and psoriatic arthritis (PsA)

Psoriasis is a chronic inflammatory skin disease caused by a complex interplay among the immune system, keratinocytes, susceptibility genes, and environmental triggers. miRNAs may be a possible class of sncRNAs which regulate psoriasis gene expression. Mounting evidence has supported miRNAs as an important triggering etiology in the pathogenesis of psoriasis as well as PsA and other chronic inflammatory conditions. miRNAs including miR-203 and miR-125b have been identified from psoriatic skin, blood, and hair samples and were found associated with non-suppressive effect. On the other hand, miR-146a is associated with psoriasis susceptibility (102).

miR-203 and miR-125b are implicated in hyperproliferative status of psoriasis. A number of authors have suggested that circulating miRNAs from blood samples can become

Table 3 Aberrant ncRNA expression-mediated pathological processes in different autoimmune diseases

Diseases	Bio-signature	Pathological process
Systemic lupus erythematosus	miR-21↑, miR-29b↑, miR-126↑ & miR-148a↑	DNA hypomethylation (68)
	miR-142-3p↓ & miR-142-5p↓	T & B cell activation (68)
	miR-146a↓	Type I IFN↑ (68)
	miR-224↑	Cell apoptosis↑ (68)
	miR-21↑, miR-31↓, miR-142-3p↓ & miR-410↓	IL-10↑ (68)
	miR-125a↓ & miR-125b↓	Th17/Treg ratio↑ (68)
	miR1273e↓& miR-3201↓	Endocapillary glomerular inflammation (72)
Rheumatoid arthritis	LOC100506036↑	T cell activation (68)
	miR-223↑	Pro/anti-inflammatory ratio↑ & cytokine imbalance (68)
	miR-21↓	Th17/Treg ratio↑ (68)
Sjögren's syndrome	hsa-miR-30b-5p↑, miR-150-5p↑, miR-155-5p↑, miR-223-5↑& miR-342-3p↑	BAFF & B cell proliferation↑ (87,88)
Anti-phospholipid syndrome	miR-19b↑ & miR-20a	VEGF & angiogenesis↑ (89)
Type 1 diabetes	miR-202-3p↑, miR-326↑ & miR-342↑	Ongoing autoimmunity (92)
	miR-34a↓ & miR-146a↓	Cytokine-mediated b-cell dysfunction (93)
Multiple sclerosis	miR-146↑ & miR-155↑	TLR-4 activation↑ (99)
Myasthenia gravis	miR-21-5p↑ & miR-150-5p↑	T cell dysfunction & hyperplastic thymus (95)
	let-7↑	TLR-7 & T cell activation↑ (95)
Graves' disease	let-7g-3p↑ & miR-339-5p↑, miR-23b-5p↓ & miR-92a-39↓	IL-1β↑, TNF-α↑ & Treg↓ (96,97)

potential biomarkers for diagnosis, monitoring disease activity and foreseeing treatment outcome in psoriasis and allied diseases (102-104).

IBDs

IBD is characterized by a chronic inflammation in the lower gastrointestinal tract. Crohn's disease and ulcerative colitis are the two main disease entities of IBD. Crohn's disease may involve the whole digestive tract, beginning from the oral cavity. In contrast, ulcerative colitis is almost confined to the lower gastrointestinal tract. Cao *et al.* (105) reviewed the role of miRNAs in IBD for diagnosis and correlation with disease activity. Some promising miRNAs including miR-19a, miR-21, miR-31, miR-101, miR-146a and miR-375 have been elaborated for general diagnosis and disease activity monitoring. In addition, a role of miRNAs in IBD-related acne prediction as well as prognosis telling has also been suggested (106).

Coeliac disease (CD)

CD is an autoimmune enteropathy triggered by the interplay between genetic predisposition (HLA-DQ2 or HLA-DQ8) and dietary gluten to induce inflammatory process and to cause bowel mucosa destruction. Dysregulated intestinal miRNA expression such as miR-31-5p, miR-192, miR-194, miR-449a and miR-638 has been reported to correlate with Wnt signaling, cell proliferation and differentiation. Felli *et al.* (107) suggested that these dysfunctional miRNAs are potentially the disease biomarker of CD.

Table 4 summarizes various ncRNA expression-mediated pathological processes in different inflammatory rheumatic diseases.

Conclusions and prospective

miRNAs are evolutionally conserved key players for cellular and developmental process in eukaryotic organism

Table 4 Aberrant ncRNA expression-mediated pathological processes in different inflammatory rheumatic diseases

Disease	Bio-signature	Pathological Process
Ankylosing spondylitis	let-7i↑	Th1 (IFN-γ) immune response↑ (100)
	miR-21↑, miR-124↑, let-7i↑ & miR-130a↓	Bone erosion↑, inflammation↑, TNF-α↑, autophagy↑ & TLR-4 down regulation (102)
Psoriasis	miR-21↓, miR-31↑, miR-125a↑ & miR-146a↑	T cell apoptosis↓
		Keratinocyte-immune interaction↑
		Chronic skin inflammation↑ &
		Epidermal differentiation↑
Psoriatic arthritis	miR-146a↑	IL-1R associated kinase↓ & TRAF-6↓ (104)
	miR-21-5p↑	Inflammatory process↑ (105)
Inflammatory bowel disease	miR-126a↑, miR146b↑ & miR-155↑	NK-kB↑ & pro-inflammatory cytokines↑ (106)
	miR-214↑ & miR-224↑	P21 expression↓ & late neoplastic progression↑ (107)
Coeliac disease	miR-31-5p↑, miR-192↑, miR194↑, miR-449a↑ & miR-638↑	Wnt signal↑, cell proliferation/differentiation↑ & adherent junction pathway↑ (108)

at the post-transcriptional level. However, these miRNA molecules target mRNA in a non-specific manner so that a miRNA can target several mRNAs, or alternatively, several miRNAs may target the same mRNA molecule. By way of microarray detection and bioinformatic analysis, miRNA expression profile may potentially become bio-signatures for etiopathogenesis, general diagnosis, disease activity, therapeutic monitoring, and prognosis. The interpretation of these bio-signatures from high throughput "omics" resulted in somewhat difficult and inconsistency. A useful disease biomarker must primarily be the disease-causing molecule with high sensitivity and specificity in predicting disease risk or monitoring the disease activity. The miRNAs can be obtained from plasma, tissue fluid, specific tissues or immune-related cells. How to direct correlate, but not only associate, miRNAs with disease entity should be considered. It is suggested miRNAs be extracted from a particular tissue (e.g., the kidney) or a particular specimen (e.g., urine or body fluid) and be compared for the cause-effect relationship between them for diagnosis, determining disease activity, therapeutic monitoring and prognosis prediction (70-73). Furthermore, the functional studies of the involved ncRNAs in the targeted tissues are equally important for understanding the pathogenesis and pathological processes of the individual disease entities.

For searching a useful disease biomarker/bio-signature, lncRNAs (>250 bp) are considered more suitable candidates than miRNAs due to their cell lineage-specificity in contrast to the pleotropic properties of miRNAs. Up to the present, only a limit of studies have been reported in autoimmune diseases such as RA (78,79). Recently, a new type of RNA, named circular RNAs (cirRNAs) based on its covalently closed structure, was extensively studied in eukaryotic cells. These cirRNAs have been found lack of terminated 5' caps and 3' tails. These molecules can compete with linear RNAs with regards to tissue specificity by regulating RNA splicing and working as endogenous sponge RNAs to bounce mRNAs (108). Li *et al.* (109) have demonstrated that plasma cirRNA profile could be used as novel bio-signature for SLE. It is expected that more and more lncRNAs and cirRNAs will be found and be used for comparison with miRNAs in different autoimmune and inflammatory rheumatic diseases in the near future. However, it is more practical at the present time to use miRNA as diagnostic biomarker by taking into account the criteria listed in *Table 1*.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/jlpm.2018.05.02). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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