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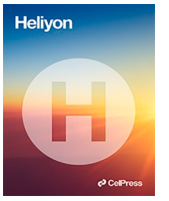

Review article

Circular RNAs: Potential biomarkers and therapeutic targets for autoimmune diseases

Ren-Jie Zhao [1], Wan-Ying Zhang [1], Xing-Xing Fan [*]

Dr. Neher's Biophysics Laboratory for Innovative Drug Discovery, State Key Laboratory of Quality Research in Chinese Medicine, Macau University of Science and Technology, Macau(SAR), China

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ABSTRACT

The outcomes and prognosis of autoimmune diseases depend on early diagnosis and effective treatments. However, symptoms of early autoimmune diseases are often remarkably similar to many inflammatory diseases, leading to difficulty in precise diagnosis. Circular RNAs (circRNAs) belong to a novel class of endogenous RNAs, functioning as microRNA (miRNA) sponges or participating in protein coding. It has been shown in many studies that patients with autoimmune diseases have aberrant circRNA expression in liquid biopsy samples (such as plasma, saliva, and urine). Thus, circRNAs are potential biomarkers for the diagnosis and prognosis of autoimmune diseases. Moreover, overexpression and depletion of target circRNAs can be utilized as possible therapeutic approaches for treating autoimmune diseases. In this review, we summarized recent progress in the roles of circRNAs in the pathogenesis of autoimmune diseases, including rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis, and type 1 diabetes. We also discussed their potential as biomarkers and therapeutic targets.

1. Introduction

Autoimmune diseases (ADs) are a group of complex chronic inflammatory diseases characterized by the deficiency of autoimmune tolerance and mistaken immune attack on healthy tissues [1]. Multiple factors have been reported to be closely related to ADs, such as host genetic alternation, continuous immune activation, and environmental pollution [2]. According to statistics, about 5%–10 % of the world population is affected by ADs, among which rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), multiple sclerosis (MS), and type 1 diabetes are the most common types [3]. Due to the remarkably similar pre-symptoms of different types of ADs, currently, there is a lack of practical laboratory markers. In recent decades, the commonly used clinical diagnostic markers include autoantibodies, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and rheumatoid factor (RF). However, these markers are not sufficiently specific, and thus, they cannot be used to diagnose ADs quickly and accurately [4]. Therefore, particular biomarkers and effective therapeutic methods for ADs are urgently required.

Noncoding RNAs (ncRNAs), including microRNAs (miRNAs), long ncRNAs (lncRNAs), and circular RNAs (circRNAs), are essential regulatory elements for gene profiling and have been found to play key roles in diverse cellular processes [5]. CircRNAs are a single-stranded RNA that forms a covalently closed continuous loop because the 3′ and 5′ ends usually present in an RNA molecule are joined together. Since circRNAs are resistant to exonuclease-mediated degradation. They are consequently more stable than other

* Corresponding author.
E-mail address: xxfan@must.edu.mo (X.-X. Fan).
[1] These authors contributed equally.

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ncRNAs in cells [6]. So far, circRNAs have been found to have diverse functions, such as serving as miRNA sponges, competing with mRNA splicing, and being involved in the transcription or post-transcription of target genes [7].

Many studies have found that circRNA is present in large amounts in body fluids such as peripheral blood, saliva, urine, semen, etc., and can be used as an ideal biological fluid for disease research [9,10]. In recent years, many studies have attempted to identify novel circRNAs and their potential biological functions in ADs since the abnormal expression levels of many circRNAs in ADs have been widely reported (Table 1). Attractively, circRNAs are not only molecular markers for disease diagnosis but also key regulators or therapeutic targets of disease occurrence and development. Therefore, research in circRNA functions within immune cells is continually expanding and some of the established functions of circRNAs in immune cells help regulate immune responses. For example, circRNAs have been found to induce dendritic cell activation and maturation, enabling them to interact with antigen-specific T cells. Furthermore, circRNA can induce significant proliferation of B cells, monocytes, and macrophage populations [8]. These findings highlight the complex regulatory networks in which circRNAs participate and suggest potential implications for the development of therapeutic strategies for immune-related diseases. Notably, this field is dynamic, and ongoing research continues to refine our understanding of circRNA function in immune cells. In this review, we summarized the recent progress of circRNAs in the pathogenesis of ADs and discussed their potential as biomarkers and therapeutic targets (Fig. 1).

2. CircRNA and RA

RA, as one of the rifest ADs in the world, is characterized by generalized inflammation in multiple joints with severe cartilage, articular deformation, and bone erosion. More severe cases can lead to interstitial pneumonia, vasculitis, and systemic complications [11]. The most effective strategy for RA treatment is early diagnosis and better prevention of disease progression. However, RA can only be diagnosed by morning joint stiffness and elevated CRP or ESR. Unfortunately, these indicators are not specific and cannot be used as a gold standard since other arthritis or ADs also present these changes. Therefore, identifying novel and reliable RA biomarkers is vital for early diagnosis and treating RA.

2.1. CircRNA expressed abnormally in body fluids and tissues

In recent years, researchers have successfully verified of several circRNAs that can promote/inhibit the development and inflammatory response of RA. As shown in Table 1, circ_0001947, circ_0003972, circ_0025908, circ_0088036, circ_0088194, circ_AFF2, circASH2L, circMAPK9, circ0088036, circ_0005008, and circ_0005198 which are isolated from peripheral blood and synovial tissues can promote the development of RA and inflammation *in vivo* by acting as different microRNA sponges to regulate the expression of

Table 1
Functions of CircRNAs in ads.

Disease	CircRNA	MiRNA	Source	Up/ Down	Function	Refs
RA	CircHIPK3	miR-149-5p			Combination therapy for circHIPK3 silence with ATO	[14]
	Circ_0001947	miR-671-5p	synovial tissues	Up	Therapeutic target	[15]
	Circ_0003972	miR-654-5p	synovial tissues	Up	Therapeutic target	[22]
	Circ_0025908	miR-137	synovial tissues	Up	Therapeutic target	[16]
	Circ_0088036	miR-1263	peripheral blood	Up	Therapeutic target	[17]
	Circ_0088194	miR-766-3p	synovial tissues	Up	Therapeutic target	[23]
	Circ_AFF2	miR-375/miR-650	peripheral blood	Up	Therapeutic target	[13,18]
	CircASH2L	miR-129-5p	synovial tissues	Up	Therapeutic target	[21]
	CircMAPK9	miR-140-3p	synovial tissues	Up	Therapeutic target	[20]
	CircEDIL3	miR-485-3p	mesenchymal stem cell		Therapeutic target	[26]
SLE	Hsa_circ_0000479		PBMC	Up	Therapeutic target	[33]
	Hsa_circ_0049224		PBMC		DNA methylation	[37]
	Hsa_circ_0049220		PBMC		DNA methylation	[37]
	Hsa_circ_0012919		PBMC	Down	biomarker	[38]
	Hsa_circ_0012919	miR-125a-3p	PBMC		Therapeutic target	[38]
	Hsa_circ_0010957	miRNA-125b	PBMC		Therapeutic target	[43]
	CircGARS		PBMC	Up	biomarker	[48]
	CircIBTK	miR-29b	PBMC	Down	biomarker	[49]
T1D	Hsa_circRNA_101062		plasma	Up	biomarker	[55]
	Hsa_circRNA_100332		plasma	Up	biomarker	[55]
	Hsa_circRNA_085129		plasma	Up	biomarker	[55]
	Hsa_circRNA_103845		plasma	Up	biomarker	[55]
	CircPPM1F			Up	Therapeutic target	[57]
	CiRS-7	miR-7		Up	Therapeutic target	[60]
	Hsa_circ_0060450	miR-199a-5p		Up	Therapeutic target	[61]
MS	Circ_0005402		PBMC	Down	Biomarker	[68]
	Circ_0035560		PBMC	Down	Biomarker	[68]

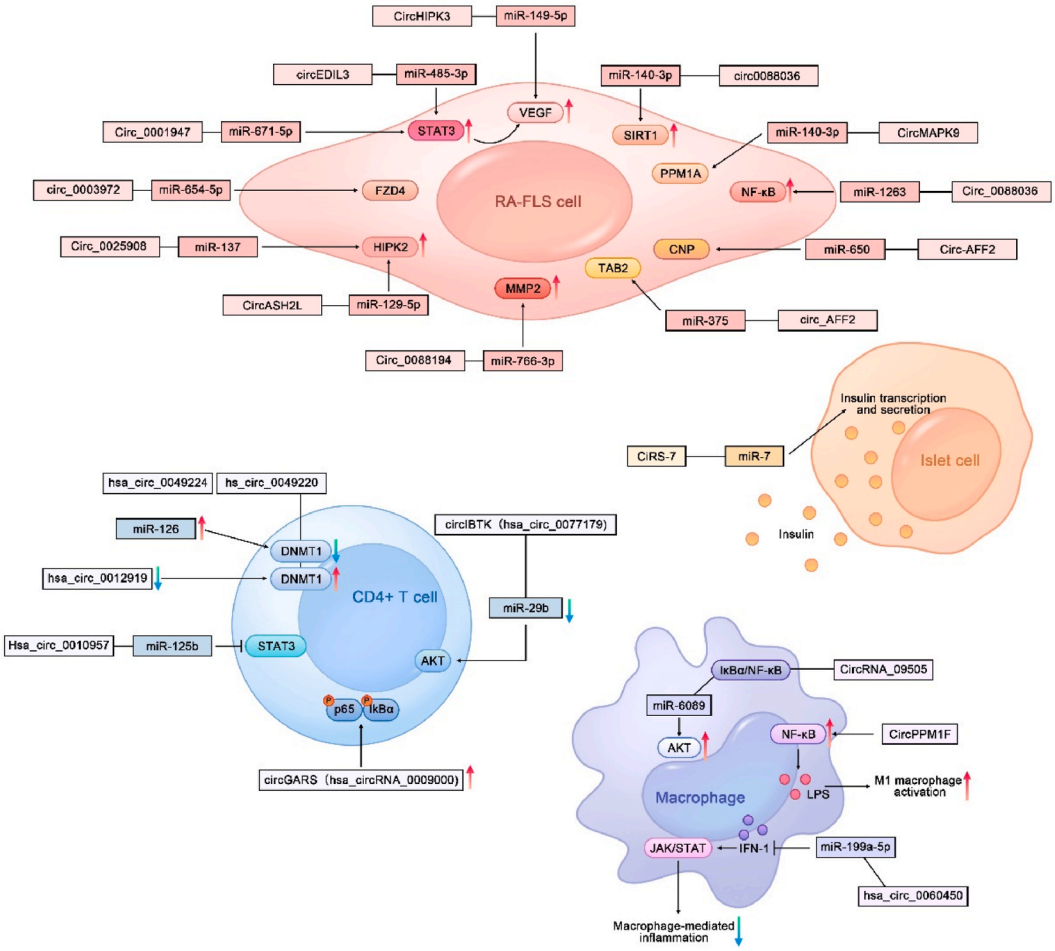

Fig. 1. The proposed regulatory roles of circular RNAs in autoimmune diseases.

related genes such as *HIPK2*, *MMP2*, *CNP* and others [12–23]. Due to their relevant roles in RA development, these circRNAs are potential targets for treating RA. However, more comprehensive studies and clinical trials are required to investigate the regulatory roles of circRNAs in treating RA.

2.2. CircRNA and vascular endothelial growth factor (VEGF) signaling

Recent studies have demonstrated that increased VEGF can enhance vascular permeability and may play a role in joint swelling and chondrocytes [24,25]. Interestingly, Zhang et al. found that circHIPK3 is markedly elevated in RA fibroblast–like synoviocytes (RA-FLS), which then affects VEGF secretion and induces the generation of synovial blood vessels. CircumHIPK3 depletion inhibits VEGF production and RA-FLS-induced angiogenesis, suggesting a role for circHIPK3 in RA-induced pathological angiogenesis [4]. Additionally, researchers discovered that arsenic trioxide (ATO) hinders VEGF activity by suppressing circHIPK3 expression in TNF-α-induced RA-FLS. According to the results, ATO inhibits vascular endothelial growth factor by targeting the circHIPK3/miR-149-5p/FOXO1 pathway. Combining reduced circHIPK3 expression with ATO presents a potential treatment for RA [14]. Similarly, circEDIL3 can be transferred across cells via mesenchymal stem cell exosomes and then promote PIAS3 expression as a sponge of miR-485-3p, thereby upregulating STAT3 activity, accelerating VEGF expression and angiogenesis in RA-FLS. CircEDIL3 improves the outcomes of RA by suppressing inflammation-induced angiogenesis and promoting pannus progression through miR-485-3p/PIAS3/STAT3/VEGF functional module *in vitro* and *in vivo*. Therefore, circEDIL3 derived from mesenchymal stem cell exosomes may be valuable agents for treating RA [26]. Taken together, researchers have identified a series of up-/down-regulated circRNAs in RA. However, the downstream pathways of the inflammatory response of these circRNAs are unclear. The exact functional mechanisms of circRNAs in RA need to be further explored and verified *in vitro* and *in vivo*.

3. CircRNA and SLE

SLE is a multi-organ autoimmune disease that affects young women more than men [27]. Similar to RA, studies have shown that SLE is closely related to the environment [28], genetics [29], and hormones [30]. However, the exact pathogenic mechanisms of SLE remain unknown. Since early symptoms of SLE are indistinguishable from RA [31], it is necessary to find new specific biomarkers that can rapidly diagnose patients with SLE. As SLE is a systematic symptom and circRNAs are widely and stably present in body fluids [32], utilizing blood samples to detect differentially expressed circRNAs in SLE is feasible and may further contribute to the early diagnosis of SLE. For instance, Guo et al. found that PBMC-derived hsa_circ_0000479 was dramatically upregulated in SLE but not in RA [33]. This result indicated that the dysregulation of circRNA is specific in SLE. Mechanistically, hsa_circ_0000479 could target Wnt-16 in SLE, a key member of the Wnt family and has been previously shown to regulate p53 activity and PI3K/AKT pathway [34].

3.1. DNA methylation

Aberrant DNA methylation in some genes of SLE patients' $CD4^+$ T cells [35,36] was frequently observed. Zhang et al. reported that DNMT1 expression was positively correlated with mRNA expression of hsa_circ_0049224 and hsa_circ_0049220 [37]. Consistently, Zhang et al. found that hsa_circ_0012919 was abnormally upregulated in $CD4^+$ T cells of SLE patients, and its downregulation increased the expression of DNMT1 [38]. In addition, they demonstrated that DNA methylation levels of CD70 and CD11a were negatively correlated with hsa_circ_0049224 and that these DNA methylation levels were significantly elevated after transfection. These results suggest that hsa_circ_0049224 may be associated with the aberrant DNA methylation present in SLE $CD4^+$ T cells. Their recent study also identified a new mechanism of hsa_circ_0012919 as a sponge for miR-125a-3p for SLE studies. hsa_circ_0012919 and MDA5 expression were detected after isolating $CD4^+$ T cells from SLE patients and healthy control subjects, as well as MDA5 promoter methylation levels. MDA5 mRNA expression was found to be associated with SLE parameters, and finally, hsa_circ_0012919 was shown to regulate MDA5 via miR-125a-3p [39].

3.2. Stat: IL-6 receptor signaling

STAT3 has been reported to be an important component of the JAK-STAT signaling pathway [40] and is involved in the pathogenesis of lupus-susceptible mice [41]. increased expression of STAT3 in SLE T cells promotes chemokine-mediated cell migration [42]. Hsa_circ_0010957 was found to take up miR-125b and increase its expression in SLE-derived $CD4^+$ T cells in a trial enrolling 30 patients diagnosed with SLE and 25 healthy individuals. Moreover, hsa_circ_0010957 blocks STAT3 signaling as a sponge of microRNA-125b, thus inhibiting the pro-inflammatory effects of IL-6 [43]. Reduced SOCS1 expression and/or increased IFN-γ/IL-6 signaling are prevalent in both [44,45].

3.3. NF-κB signaling

Transcription factors of the nuclear factor κB (NF-κB)/Rel family play a pivotal role in inflammatory and immune responses [46,47]. Zhao et al. demonstrated that overexpression of PBMC-derived cricGARS (hsa_circRNA_0009000) in SLE suppressed the expression of the ubiquitin editing enzyme A20 and facilitated the phosphorylation of p65 and IkBα [48], thereby activating NF-κB pathway-mediated immune inflammatory responses in SLE. Hence, circGARS can be used as a potential biomarker for SLE.

3.4. T Cell Receptor signaling

T Cell Receptor (TCR) activation promotes several signaling cascades that ultimately determine cell fate through regulating cytokine production, which also includes the AKT pathway. Wang et al. found that circIBTK (hsa_circ_0077179) was downregulated in SLE, and they also demonstrated that miR-29b activated the AKT pathway while inducing DNA demethylation, but binding of circIBTK to SLE-derived miR-29b reversed this result [49]. This suggests that circIBTK and miR-29 are potential biomarkers and therapeutic targets for SLE. These results illustrating the pathogenesis of SLE and provided new ideas and insights for subsequent studies to identify potential biomarkers and therapeutic targets.

4. CircRNA and type 1 diabetes

Type 1 diabetes (T1D) is a typical AD that affects approximately 78,000 youths each year [50]. T1D is due to the destruction of the insulin-producing β-cells [51]. T1D usually happens in childhood but can also occur in adults [52]. According to the registries in Europe, babies aged 0–4 years old have the highest incidence rate of T1D [53]. For early diagnosis of T1D, it is therefore crucial to identify specific biomarkers.

4.1. Abnormal expressions of CircRNA in peripheral blood

Luo et al. reported that 30 upregulated and 63 downregulated circRNAs have been detected in the peripheral blood of patients with T1D, and two circRNAs (hsa_circ_0002473 and hsa_circ_0072697) have been proven with reverse transcription-PCR [54]. In addition, the GO and KEGG analyses revealed that these circRNAs were primarily associated with the non-homologous end-joining, RIG-I-like

receptor signaling pathway, NF-κB signaling pathway, and cell cycle, which are related to the development of T1D [54]. Another study by Li et al. proved that four circRNAs (hsa_circRNA_101062, hsa_circRNA_100332, hsa_circRNA_085129, and hsa_circRNA_103845) in the plasma of patients with new onset T1DM were significantly upregulated [55]. Interestingly, circRNAs can regulate gene expression by interacting with miRNAs. Pang et al. noted that signals hsa_circ0005630-miR-1247-5p-ATXN1/ARL6IP1 and hsa_circ0007026-miR-324-5p-NCAPD2/PGAM1 might be involved in the progression of T1D [56]. These studies strongly suggested that aberrant expression circRNAs are associated with the progression of T1D, and these circRNAs might be biomarkers for T1D diagnosis.

4.2. Inflammatory response and signaling pathway

Some other circRNAs are involved in the inflammatory response and signaling pathways of T1D. The circPPM1Fis, primarily found in monocytes and showing increased expression in individuals with T1DM, has the ability to stimulate M1 macrophages through the circPPM1F-HuR-PPM1F–NF-κB pathway [57]. In the early stages of T1D, the number of early macrophages skyrockets [58]. Therefore, inhibition of circPPM1F might be able to treat the early stages of T1D. Like many circRNAs are known to act as sponges for miRNAs [59], Cdr1as (also known as CiRS-7) was proposed to be a sponge for miR-7 to regulate insulin transcription and secretion in islet cells [60]. Also, hsa_circ_0060450 is upregulated in peripheral blood mononuclear cells (PBMC) as a sponge of miR-199a-5p, inhibiting the JAK-STAT signaling pathway triggered by IFN-I and thus suppressing macrophage-mediated inflammatory response [61].

Taken together, cricRNAs appear to play some regulatory roles in T1D. However, further studies are required to fully establish the functional roles of T1D treatment.

5. CircRNA and MS

MS is a central nervous system (CNS) AD that manifests as inflammatory demyelination and axonal damage [62]. MS is associated with genetic factors [63], environmental influences [64], autoimmune responses, and viral infections [65]. Recent studies have shown that differential expression of non-coding RNAs was observed in MS patients. Moreover, since circRNAs serve as microRNA sponges [66], circRNAs might be key factors in the epigenetic regulation of MS [67].

5.1. Serum circRNAs

In an analysis of circRNA expression profiles, Iparraguirre L et al. identified that circ_0005402 and circ_0035560 were under-expressed in MS patients, suggesting that circRNAs may be promising biomarkers for MS [68].

Some studies have shown a pathogenic association between mistakenly spliced genes and MS. Cardamone, G. et al. found an association between wrongly sliced GSDMB gene in MS and upregulated PBMC-derived circRNAs in MS [69]. In another circRNA experiment, some differentially expressed circRNAs were found to be related to alternative splicing of lncRNA MALAT1 [70].

5.2. CircRNAs in Th17 transformation

$CD4^+$ T cells can be differentiated into four cell types: Th1, Th2, Treg, and Th17. In different cytokine environments and under certain conditions, each Th cell type can be transformed into each other, thus keeping the body's immune responses balanced. Unlike traditional Th1 and Th2 cells, Th17 cells are primarily characterized by IL-17 secretion and are involved in the pathogenesis of ADs and chronic inflammation. Differentiated Th17 cells are plastic and can transform into other subpopulations under appropriate stimuli. For example, Th17 cells can be transformed into Th1/Th17 cells upon induction of IFN-γ and IL-12. Importantly, circRNAs are heavily involved in the differentiation and functions of Th1/Th17 cells [71]. Han et al. found that circINPP4B is associated with experimental autoimmune encephalomyelitis (EAE) progression and is upregulated in Th17 cells. CircINPP4B can act as a sponge to directly target miR-30a to regulate Th17 differentiation. This evidence thus provides a potential diagnostic and therapeutic target for Th17-mediated MS [72].

6. Perspectives

Since circRNAs are abundant, stable-expressed, and tissue-specific non-coding RNAs, A lot of effort has been put into studying their functions and related mechanisms. Recently, that a number of clinical studies have demonstrated that circRNAs are sensitive and reliable biomarkers for the diagnosis of autoimmune diseases. Furthermore, circRNAs can be potential targets in treating those diseases. However, due to the limited clinical study, researchers still have a long way to go to make circRNAs-related therapy feasible.

How to deliver circRNAs to patients is also important in clinical trials. The current delivery methods lack tissue specificity and therapeutic efficacy. Therefore, it is a essential way to discover new methods of circRNA delivery further in the future.

The use of circRNA for vaccine development is also a promising area. A study by Wang et al. found that circRNA-based technology can be used in SARS-CoV-2 vaccination [73]. CircRNAs can be packaged and delivered using nano delivery and exosomes [74,75]. Nanoparticle delivery can improve the targeting of therapeutic agents to specific cells [76].

To date, more than 20,000 circRNAs can be found in public databases [76], suggesting that computer-assisted strategies are a good means to model and facilitate genome-wide identification and prediction of circRNAs and improve the efficiency of circRNA in diagnosis and prognosis [77,78]. However, circRNA-based therapeutic approaches have only been performed in preclinical studies.

Many questions remain to be addressed in this field, including the unpredictable off-target effects of circRNA mis-splicing the immunogenicity of synthetic circRNAs [79]. Nonetheless, circRNAs undoubtedly play crucial roles in autoimmune diseases and are promising in biomarker identification and therapy development.

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CRediT authorship contribution statement

Ren-Jie Zhao: Conceptualization, Data curation, Methodology, Writing – original draft, Writing – review & editing. **Wan-Ying Zhang:** Conceptualization, Funding acquisition, Writing – review & editing. **Xing-Xing Fan:** Conceptualization, Data curation, Writing – original draft, Writing – review & editing.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:Xing-Xing Fan reports financial support was provided by Macau Science and Technology Development Fund project.

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