Pathology - Research and Practice 251 (2023) 154912

Contents lists available at ScienceDirect

Pathology - Research and Practice

journal homepage: www.elsevier.com/locate/prp

Review

Circular RNAs and inflammation: Epigenetic regulators with diagnostic role

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ARTICLE INFO

Keywords:
CircRNA
Inflammation
Biomarker
Expression
Diagnostic

ABSTRACT

Circular RNAs (circRNAs) are a group of transcripts generally known to be non-coding transcripts, but occasionally producing short peptides. Circ_Ttc3/miR-148a, circ_TLK1/miR-106a-5p, circ_VMA21/miR-9–3p, circ_0068,888/miR-21–5p, circ_VMA21/miR-199a-5p, circ_AFF2/miR-375, circ_0008360/miR-135b-5p and circ-FBXW7/miR-216a-3p are examples of circRNA/miRNA pairs that contribute in the pathogenesis of immune-related conditions. CircRNAs have been found to regulate function of immune system and participate in the pathophysiology of immune-related disorders. In the current study, we searched PubMed and Google Scholar databases until July 2022 with the key words "circRNA" OR "circular RNA" AND "inflammation". Then, we assessed the abstract of retrieved articles to include original articles that assessed contribution of circRNAs in the pathoetiology of inflammation and related disorders. Finally, we went through the main texts of the articles and tabulated the available information. Therefore, the current study summarizes the role of circRNAs in the pathoetiology of sepsis, atherosclerosis, rheumatoid arthritis and osteoarthritis, immune-related cardiovascular, pulmonary, gastrointestinal and nervous system disorders.

1. Introduction

The immune system comprises a multi-faceted network that preserves the physiological homeostasis of the internal environment of the body. The hyperactivity of this system leads to injury to the body tissues, whereas its hypo-activity results in failure of effective responses against invading pathogens [12,13,48,52]. Thus, it is crucial to investigate the immune responses and molecular pathways in this complex system. Circular RNAs (circRNAs) are a group of transcripts generally known to be non-coding transcripts, but occasionally producing short peptides. They have been found to affect activity of almost all aspects of immune system, including cellular and humoral responses [11,14,15]. They participate in the pathology of immune-related disorders and response to viral infections [61]. These transcripts have an especial structure made by a covalent closed loop between two ends of RNA without 5′ end caps and 3′ Poly (A) tails [46,53]. The history of circRNAs goes back to 1976 when they were initially identified in RNA viruses [47]. Subsequent studies showed their presence in the cytoplasm of eukaryotes [20] and mitochondria of yeast [1]. The main mechanism of circRNAs biogenesis is “back-splicing” of the precursor mRNAs in which a

Abbreviation: LPS, Lipopolysaccharide; HMGB1, High Mobility Group Box 1; TXNIP, Thioredoxin Interacting Protein; TOP1, Topoisomerase 1; RPS3, Ribosomal Protein S3; OGD, Oxygen-Glucose Deprivation; MyD88, Myeloid Differentiation Primary Response 88; HBEC, Human Bronchial Epithelial Cells; HCMs, Human-derived cardiomyocytes; WI-38, Human Embryonic Lung Fibroblast Cells; MPVECs, Primary Murine Pulmonary Microvascular Endothelial Cells; PDLCs, Periodontal Ligament Cells; RAW264.7, Leukemia Cells in Mouse Macrophages; HUVECs, Umbilical Vein Endothelial Cell; LX2, Human Hepatic Stellate Cell Line; PBMCs, Peripheral Blood Mononuclear Cells; VSMCs, Vascular Smooth Muscle Cells; MSCs, Mesenchymal Stem Cell; ox-LDL, oxidized low-density lipoprotein.

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https://doi.org/10.1016/j.prp.2023.154912
Received 12 September 2023; Received in revised form 18 October 2023; Accepted 26 October 2023
Available online 26 October 2023
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downstream 5′ splice donor is linked to an upstream 3′ splice acceptor [7]. Three types of circRNAs, namely exonic circRNAs, intronic circRNAs and exon–intron circRNAs have been recognized with the first one being the most abundant one [7]. CircRNAs contribute to the etiology of complex human pathologies including cancer [14,16]. These transcripts regulate expression of genes, mainly through sponging miRNAs [77]. Remarkably, circRNAs are regarded as modulators of immune response that are associated with the development of autoimmune disorders [80]. Participation of circRNAs in the pathophysiology of autoimmune diseases is mainly exerted through acting as miRNA sponges and further regulating a variety of cellular processes [80]. Notably, circRNAs may have tens of binding sites for miRNAs showing their high efficacy in sequestering miRNAs. Further evidence for possible role of circRNAs in the regulation of immune response has come from the observed cell-specific expression pattern of circRNAs in human hematopoietic progenitors and their differentiated progeny [38]. In the current study, we summarize the role of circRNAs in the pathoetiology of sepsis, atherosclerosis, rheumatoid arthritis (RA) and osteoarthritis, immune-related cardiovascular, pulmonary, gastrointestinal and nervous system disorders.

2. Methods

In order to find the relevant literature, we searched PubMed and Google Scholar databases until July 2022 with the key words "circRNA" OR "circular RNA" AND "inflammation". Then, we assessed the abstract of retrieved articles to include original articles that assessed contribution of circRNAs in the pathoetiology of inflammation and related disorders. Finally, we went through the main texts of the articles and tabulated the available information.

2.1. Sepsis

Sepsis is an abnormal response of immune system to infections that can result in organ failure and death. The immune responses during sepsis are described by a cytokine-mediated hyperinflammatory stage and a succeeding immune-suppressive stage which is characterized by apoptotic diminution of immune cells, enhanced T regulatory responses and increased myeloid-derived suppressor cells [2]. Several immune-related molecules including circrNAs have been found to affect aberrant immune responses and their consequences. Most of the studies in this field have been conducted in animal models. For instance, experiments in cecal ligation and puncture (CLP) models of acute kidney injury (AKI) have shown down-regulation of CIRC-Ttc3 in renal tissues. Notably, forced up-regulation of CIRC-Ttc3 could improve inflammatory response and oxidative stress markers in these animals. Mechanistically, CIRC-Ttc3 binds to sequester miR-148a and subsequently regulate expression of Rcan2. Up-regulation of miR-148a has reversed the effects of CIRC-Ttc3 on sepsis-induced AKI. Cumulatively, CIRC-Ttc3 can be a possible target for treatment of sepsis-induced AKI [64]. Another study in a similar model of AKI has demonstrated over-expression of circTLK1. Short hairpin (sh)RNA-mediated silencing of circTLK1 could reverse the effects of CLP on urine levels of NGAL and Kim-1 and serum levels of BUN and creatinine and reduce CLP-associated AKI. CircTLK1 silencing has suppressed oxidation stress, inflammatory responses, and apoptosis in the rat model of sepsis-associated AKI. Furthermore, circTLK1 silencing could decrease the effects of lipopolysaccharide (LPS) treatment on production of inflammatory cytokines and attenuate LPS-induced apoptosis in HK-2 cells. Mechanistically, circTLK1 has been shown to increase HMGB1 expression through sequestering miR-106a-5p [64]. CircVMA21 is another circRNA that could ameliorate sepsis-related AKI through regulation of miR-9–3p/SMG1 [50] and miR-199a-5p/NRP1 axes [30] (Fig. 1). Moreover, circ_0068, 888 has been shown to protect against LPS-induced HK-2 cell injury through sequestering miR-21–5p [57]. Finally, circ_0001105 has been found to protect the intestinal barrier of septic rats through suppression of YAP1 expression and inhibition of inflammatory responses and oxidative damage and [35]. Table 1 shows the impact of circRNAs in septic-related diseases.

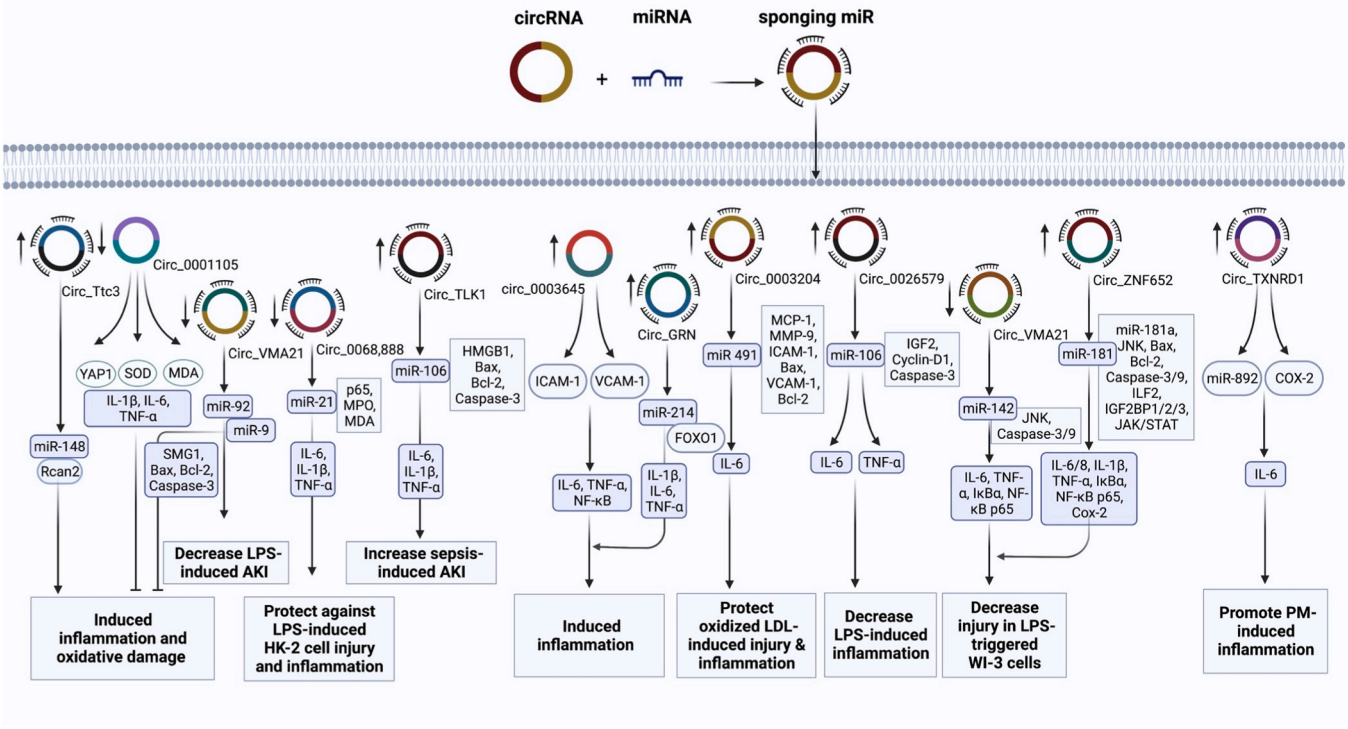

Fig. 1. Impacts of circRNAs in the septic-related diseases, atherosclerosis (AS), and immune-related pulmonary disorders. CircRNAs are involved in regulating inflammation, oxidative damage, cell injury, and PM-induced inflammation.

Table 1
Impact of circRNAs in septic-related diseases.

Disease	Circular RNA	Human/ Animal Study	Cell Culture	Inflammatory-Related Targets	Targets & Pathways	Observation	Refs.
Sepsis-Induced Acute Kidney Injury (AKI)	Circ_Ttc3 (-)	SD Rats	Renal tubular epithelial cells	Interleukin (IL)−6, IL-1β, TNF-α, iNOS	miR-148a, Rcan2	Circ_Ttc3 via regulating the miR-148a/Rcan2 axis could alleviate inflammation and oxidative stress.	[64]
Sepsis-Induced AKI	Circ_TLK1 (Up)	SD Rats	HK-2, 293T	IL-6, IL-1β, TNF-α	miR-106a-5p, HMGB1, Bax, Bcl-2, Caspase-3	Circ_TLK1 by regulating oxidative stress and inflammation via the miR-106a-5p/HMGB1 axis could increase sepsis-induced AKI.	[64]
Sepsis-Induced AKI	Circ_VMA21 (-)	Wistar rat	HK-2	IL-6, IL-1β, TNF-α	miR-9–3p, SMG1, Bax, Bcl-2, Caspase-3	Circ_VMA21 via targeting the miR-9–3p/SMG1 axis could improve AKI and decrease inflammation and oxidative stress;	[50]
Sepsis-Induced AKI	Circ_0068,888 (-)	-	HK-2	IL-6, IL-1β, TNF-α	miR-21–5p, p65, MPO, MDA	Circ_0068,888 via sponging miR-21e5p could protect against LPS-induced HK-2 cell injury and inflammation.	[57]
Sepsis-Induced AKI	Circ_VMA21 (Down)	-	THP-1, 293T	IL-1β, IL-6, TNF-α,	miR-199a-5p, Neuropilin-1, Bcl-2, Bax, Caspase-3	Circ_VMA21 by targeting the miR-199a-5p/ NRP1 axis could reduce LPS-induced AKI in a septic condition.	[30]
Sepsis	Circ_0001105 (Down)	Male SD Rats	-	IL-1β, IL-6, TNF-α	YAP1, SOD, MDA	Circ_0001105 through suppression of inflammation and oxidative damage via the YAP1 could protect the intestinal barrier of septic rats.	[35]

2.2. Atherosclerosis

Atherosclerosis is resulted from the accumulation of fats, cholesterol and other elements in and on the arteries. A bulk of evidence from experimental and clinical assays indicates that atherosclerosis is a chronic inflammatory disorder. First, T and B cells have been found in the atherosclerotic plaques [59]. Besides, both innate and adaptive immune responses have been shown to accelerate or induce atherosclerosis [59]. T cells mainly populate atherosclerotic lesions and are enriched in the fibrous cap. These cells are recruited via chemokine receptors CCR5 and CXCR6. T-helper cells have a multi-faceted role in the atherosclerosis and their functions depend on certain transcriptional programs and cytokine profiles that can either induce or reduce atherosclerosis [59].

Moreover, genome-wide association studies, advanced technologies conducted in animal models and clinical investigations have verified contribution of innate and adaptive immune systems in this condition [59]. Circ_0003645 is an example of circRNAs with differential expression in the process of atherosclerosis. This circRNA has been found to be over-expressed patients with atherosclerosis and in HUVECs exposed to oxLDL. Circ_0003645 silencing has resulted in inhibition of LDH leakage and cell apoptosis, and reduction in expressions of IL-6, TNF-α, ICAM-1, VCAM-1 and NF-κB. Moreover, cell viability has been increased after circ_0003645 silencing. Taken together, circ_0003645 silencing could alleviate atherosclerosis-related inflammatory responses and apoptosis, while promoting viability of endothelial cells upon exposure with oxLDL through modulation of NF-κB pathway [43]. Circ_GRN is another circRNA that promotes proliferative ability and invasion of human VSMCs. Expression of circ_GRN has been shown to be increased in the serum of patients with atherosclerosis and ox-LDL-exposed human VSMCs. Circ_GRN silencing could reverse ox-LDL-induced cell proliferation, migration, and inflammation. Mechanistically, circ_GRN could bind with miR-214–3p to regulate expression of FOXO1. miR-214–3p suppression could attenuate the protective impact of circ_GRN silencing on ox-LDL-exposed human VSMCs; wile miR-214–3p up-regulation could abolish ox-LDL-induced proliferation and migration of human VSMCs [29]. Similarly, circ_0003204 silencing has been shown to protect endothelial cells against ox-LDL-associated cellular damage through influencing miR-491–5p/ICAM1 axis [73] (Fig. 1). Table 2 shows the impact of circRNAs in atherosclerosis.

2.3. Rheumatoid Arthritis (RA)

Aberrations in the regulation of humoral and cellular immune responses have been detected in RA [24]. Therefore, circRNAs that regulate activity of each of these mechanisms can possibly affect pathogenesis of RA. Wen et al. have assessed expression of inflammation-related circRNAs in peripheral blood mononuclear of RA patients and normal subjects resulting in identification of circ_0003353, circ_0005732, circ_0072428 and circ_ 0091685 as differentially expressed circRNAs between two groups. Hsa_circ_0003353 has also been found to be over-expressed in RA-fibroblast-like synoviocytes (FLSs). This circRNA has been shown to participate in enhancement of inflammatory responses, synovial invasion, and joint destruction in the context of RA [58]. Circ_AFF2 is another circRNA that can facilitate proliferation and inflammatory responses of FLSs through influencing miR-375/TAB2 axis [76]. On the other hand, circ_0008360 has been shown to inhibit proliferation, migration, and inflammation of these

Table 2
Impact of circRNAs in atherosclerosis (AS).

Circular RNA	Human/Animal Study	Cell Culture	Inflammatory-Related Targets	Targets & Pathways	Observation	Refs.
circ_0003645 (Up)	21 pairs of AS samples and adjacent normal tissues	HUVECs	IL-6, TNF-α, NF-κB	ICAM-1, VCAM-1	Silencing of circ_0003645 via the NF-κB pathway could alleviate inflammation in endothelial cells induced by ox-LDL.	[43]
Circ_GRN (Up)	AS blood samples (n = 35), healthy blood samples (n = 35)	HVSMCs	IL-1β, IL-6, TNF-α	miR-214–3p, FOXO1	Circ_GRN via targeting the miR-214–3p and FOXO1 could increase inflammation of vascular smooth muscle cells in AS.	[29]
Circ_0003204 (Up)	-	HUVECs	IL-6	miR-491–5p, MCP-1, MMP-9, ICAM-1, Bax, VCAM-1, Bcl-2	Knockdown of circ_0003204 by targeting miR-491–5p/ ICAM1 axis could protect HUVECs against oxidized LDL-induced injury and inflammation.	[73]

cells and induce their apoptosis through regulation of miR-135b-5p/HDAC4 axis [18]. Finally, circFBXW7 is a circRNA originated from mesenchymal stem cells exosomes that can attenuate proliferation, migratory potential and inflammatory responses of FLSs though targeting miR-216a-3p/HDAC4 axis [4] (Fig. 2). Table 3 shows the impact of circRNAs in RA.

2.4. Osteoarthritis

Osteoarthritis is a degenerative disorder of joints that is associated with dysregulation of several pathways. CiRS-7 expression has been found to be reduced in blood samples of patients with osteoarthritis parallel with up-regulation of miR-7 expression. Expression of this circRNA has also been reported to be reduced in chondrocytes upon treatment with IL-1β. This treatment has also suppressed proliferation of chondrocytes and increased release of inflammatory cytokines. Small interfering (si)RNA-mediated suppression of ciRS-7 and miR-7 mimics could enhance the effect of IL-1β on release of inflammatory cytokines and cell apoptosis. Thus, ciRS-7/miR-7 axis has been regarded as a regulator of chondrocytes proliferation, apoptosis and inflammation [79]. Circ_0128846 is another circRNA that enhances osteoarthritis progression through regulation of miR-127–5p/NAMPT axis [33]. Similarly, circ_0134111 has a role in the pathoetiology of this disorder, since its silencing in chondrocytes has been found to relieve IL-1β-associated apoptosis, inflammatory responses and extracellular matrix degradation through miR-515–5p/SOCS1 axis [60]. On the other hand, hsa_circ_0005567 has been demonstrtaed to promote polarization of macrophages toward M2 phenotype through modulation of miR-492/SOCS2 axis, thus inhibiting progression of osteoarthritis [72]. In fact, M2 macrophages are alternatively activated macrophages that have functions in homeostatic and repair emechanisms. These macrophages have anti-inflammatory and tumorigenic effects [45]. Table 4 shows the impact of circRNAs in osteoarthritis.

2.5. Pulmonary disorders

Different experiments in the context of pneumonia have shown dysregulation of circRNAs and their role in the pathogenesis of this disorder. For instance, circ_0026579 silencing has been shown to alleviate LPS-induced inflammation injury in a cell line originated from embryonic lung tissue through modulation of miR-24–3p/IGF2 axis [71]. On the other hand, circVMA21 has been found to have a protective effects against LPS-induced WI-38 cells injury through modulation of expression of miR-142–3p [67]. CircANKRD36 is another circRNA that participates in the LPS-mediated cell injury through regulation of miR31–3p expression [17] (Fig. 1).

The effects of circRNAs on PM2. 5-induced inflammatory responses in the lung tissue has also been investigated. For instance, circ_406961 has been shown to interact with ILF2 to influence PM2. 5-induced inflammatory response in human bronchial epithelium through induction of activity of STAT3/JNK pathway [25]. Furthermore, circTXNRD1 has been demosntrtaed to promote ambient particulate matter-associated inflammatory response in these cells through regulation of miR-892a/COX-2 axis [54]. Table 5 shows the impact of circRNAs in immune-related pulmonary disorders.

2.6. Gastrointestinal disorders

Inflammatory bowel disease (IBD) is a prototype if immune-related gastrointestinal disorders in which expression of circRNAs has been found to be changed. A high throughput circRNA expression profiling has indicated the importance of several circRNA/miRNA/mRNA axes in the pathogeensis of IBD [78]. Moreover, another study has shown association between expression levels of circular CDKN2B-AS1 and IBD and its imporatnce in the formation of intestinal barrier [44]. Altered expression of circRNA_103516 is regarded as a biomarker for IBD. Its expression has been correlated with Crohn's disease activity index (based on some clinical data, including the number of soft stools, abdominal pain, general condition, presence of complicationor an abdominal mass) and levels of inflammatory markers CRP, ESR, TNF-α

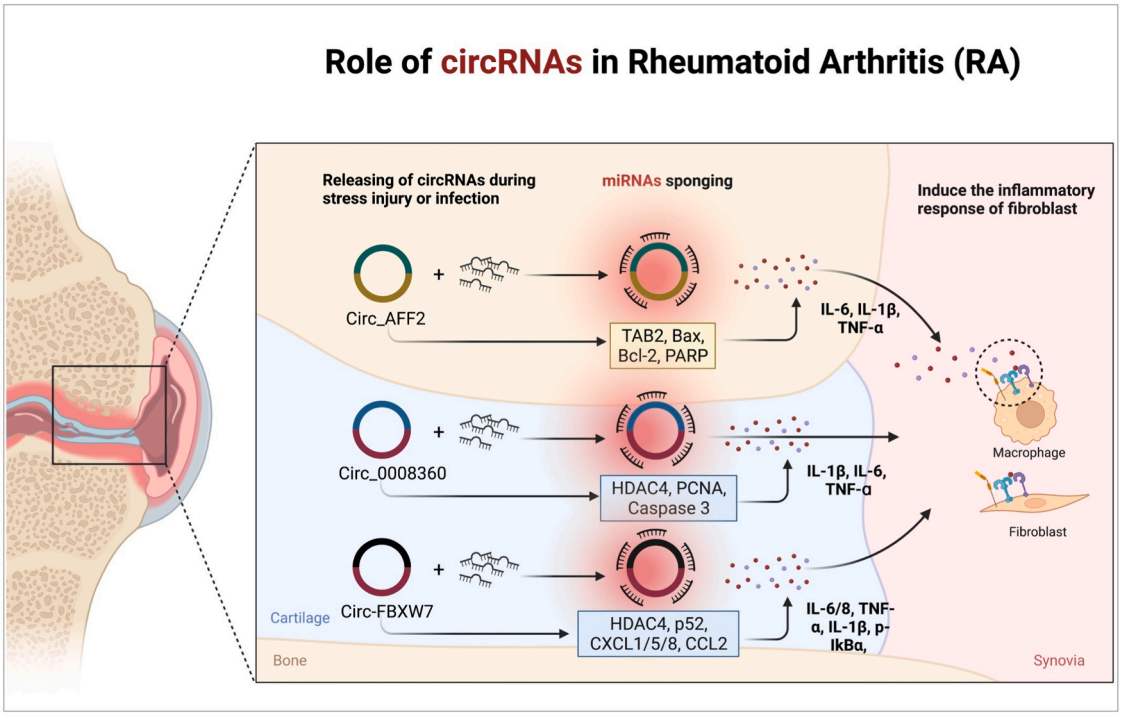

Fig. 2. Rheumatoid arthritis (RA) and the role that specific signaling pathways played by circRNAs in the development of the disease. CircRNAs contribute to the control of immune cells and inflammatory response cells, both of which are part of the body's immune system.

Table 3
Impact of circRNAs in Rheumatoid Arthritis (RA).

Circular RNA	Human/Animal Study	Cell Culture	Inflammatory-Related Targets	Targets & Pathways	Observation	Refs.
hsa_circ_0003353 (Up)	Synovial tissue samples, RA patients (n = 20)	PBMCs, immortalized fibroblast-like synoviocyte cell	IL-1β, IL-4, IL-6, IL-8, IL-10, TNF-α	-	Expression of hsa_circ_0003353 could be related to inflammation in patients with RA.	[58]
Circ_AFF2 (Up)	Peripheral blood samples: RA (n = 39), normal (n = 28)	FLS-Normal, FLS-RA	IL-6, IL-1β, TNF-α	miR-375, TAB2, Bax, Bcl-2, PARP	Circ_AFF2 via the miR-375/TAB2 axis could induce the inflammatory response of fibroblast-like synoviocytes in RA.	[76]
hsa_circ_0003353 (Up)	Synovial tissue samples, RA patients (n = 20)	PBMCs, immortalized fibroblast-like synoviocyte cell	IL-4/6/8/10, IL-1β, TNF-α	-	Expression of hsa_circ_0003353 could be related to inflammation in patients with RA.	[58]
Circ_0008360 (Down)	synovial tissue samples: RA (n = 39), normal (n = 14)	Normal-FLSs, RA-FLSs	IL-1β, IL-6, TNF-α	miR-135b-5p, HDAC4, PCNA, Caspase-3	Circ_0008360 by targeting the miR-135b-5p and HDAC4 could increase apoptosis and decrease inflammation of fibroblast-like synoviocytes in RA.	[18]
Circ-FBXW7 (Down)	Synovial tissue samples: RA (n = 30), normal (n = 30), Lewis rats	MH7A, MSCs	IL-6/8, TNF-α, IL-1β, p-IkBα,	miR-216a-3p, HDAC4, p52, CXCL1/5/8, CCL2	MSCs–originated exosomal circ-FBXW7 via targeting miR-216a-3p and HDAC4 could Attenuate inflammation of fibroblast-like synoviocytes in RA.	[4]

Table 4
Impact of circRNAs in osteoarthritis (OA).

Circular RNA	Human/Animal Study	Cell Culture	Inflammatory-Related Targets	Targets & Pathways	Observation	Refs.
ciRS-7 (Down)	OA blood samples (n = 20), healthy blood samples (n = 20)	C28/I2	IL-6/8/10, TNF-α	miR-7, Bax, Bcl-2, Caspase-9	The ciRS-7/miR-7 axis could be a regulator in inflammation in chondrocytes.	[79]
Circ_0128846 (Up)	OA cartilage tissues (n = 21), normal tissues (n = 8)	Chondrocytes	TNF-α, IL-1β, IL-6,	miR-127–5p, NAMPT, MMP3, Collagen-II, Bcl-2, Bax, Caspase-3, PARP	Knockdown of circ_0128846 by targeting the miR-127–5p/NAMPT axis could inhibit ECM degradation, inflammation, and apoptosis in OA chondrocytes.	[33]
Circ_0134111 (Up)	OA tissue samples (n = 22), healthy tissue samples (n = 15)	HCs	IL-1β, IL-6	miR-515–5p, SOCS1, Bax, Bcl-2, caspase-3, MMP-13, ADAMTS5, collagen II	knockdown of circ_0134111 via targeting miR-515–5p/SOCS1 axis could relieve IL-1β-induced changes in human chondrocytes.	[60]
hsa_circ_0005567 (Down)	Synovial tissues: OA (n = 15), control (n = 15)	THP-1, HNCs	TNF-α, IL-1β, IL-10, iNOS	miR-492, SOCS2, Arg-1, Caspase-3, Bax, Bcl-2	Hsa_circ_0005567 overexpression via modulating miR-492/SOCS2 axis to inhibit OA progression could promote M2 type macrophage polarization.	[74]
Circ-ANKRD36 (Down)	OA tissue samples (n = 39) and healthy tissue (n = 9)	Chondrocyte	IL-1β, TNF-α, IL-6/8	miR-599, Casz1, Bax, Bcl-2, Caspase-3, PARP-1	Circ-ANKRD36 via regulation Casz1 by targeting miR-599 expression could prevent OA chondrocyte apoptosis and inflammation.	[60]
Circ-SEC24A (Up)	Cartilage tissue samples: OA (n = 30), normal (n = 30)	Chondrocyte	IL-1β, TNF-α, IL-6	miR-142–5p, SOX5	Circ-SEC24A by regulating miR-142–5p/SOX5 axis could promote IL-1β-induced apoptosis and inflammation in chondrocytes.	[49]
Circ-ZNF652 (Up)	Synovial fluid samples: OA (n = 60), control (n = 60)	Chondrocyte	NF-κB	MMP-13, PTEN	Overexpression of circ-ZNF652 by up-regulating PTEN could positively regulate LPS-induced apoptosis in OA of chondrocytes.	[72]
has_circ_0000448 (Up)	TMJ synovial tissues (n = 5)	-	TNF-α	-	In temporomandibular joint osteoarthritis (TMJOA), overexpression of has_circ_0000448 via the CeRNA mechanism could increase TNF-α secretion of the synovium.	[21]
Circ_HIPK3 (Up)	GA (n = 30), normal (n = 30), C57BL/6 mice	PBMCs, FMCs, THP-1, 293T	IL-1β, TNF-α, TLR4, NLRP3, p65, p-IkBα	miR-561, miR-192, Caspase-1	Circ-HIPK3 via sponging miR-561 and miR-192 could enhance TLR4 and macrophage NLRP3 inflammasome in gouty arthritis (GA).	[32]

and and IFN-γ. Moreover, Additionally, circRNA_103516 levels have been correlated with stricturing and penetrating behaviour. Hsa-miR-19b-1–5p has been suggested to exeert these functions through sponging hsa-miR-19b-1–5p [70].

CircRNA RSF1 is involved in the pathoetiology of radiation-induced liver disease, since it increase the inflammatory and fibrotic features through modulation of miR-146a-5p expression [8]. Finally, hsa_circ_0093884 binding with RPS3 has been found to ameliorates inflammatory responses in hepatocytes [27]. Table 6 shows the impact of circRNAs in immune-related gastrointestinal disorders.

2.7. Cardiovascular disorders

CircRNAs have been shown to affect pathophysiology of myocarditis, myocardial infarction, atherosclerotic cardiovascular disease and abdominal auortic aneurism (Table 7). For instance, circACSL1 can aggravate myocardial inflammation and cellular damage through regulating miR-8055/MAPK14 axis [75]. Circ_0050908 has a similar effect in this disorder through up-regulating TRAF3 by sponging miR-324–5p [27].

CircMAT2B has an established role in aggravation of oxygen-glucose deprivation-induced inflammatory damage via sponging miR-133 [23].

Table 5
Impact of circRNAs in immune-related pulmonary disorders.

Disease	Circular RNA	Human/ Animal Study	Cell Culture	Inflammatory-Related Targets	Targets & Pathways	Observation	Refs.
Pneumonia	Circ_0026579 (Up)	-	WI-38	IL-6, TNF-α	miR-24–3p, IGF2, Cyclin-D1, Caspase-3	Knockdown of Circ_0026579 via the miR-24–3p/IGF2 axis could alleviate LPS-induced inflammation.	[71]
Pneumonia	Circ_VMA21 (-)	-	WI-38	IL-6, TNF-α, IκBα, NF-κB p65	miR-142–3p, JNK, Caspase-3/9	Circ_VMA21 via the miR-142–3p-NF-κB/JNK axis could protect WI-38 cells against LPS.	[67]
Pneumonia	Circ_ANKRD36 (Up)	-	MRC-5	IL-6/8/34, TNF-α, IκBα, NF-κB p65	miR-31–3p/5p, MyD88, Caspase-3/9	Knockdown of circ-ANKRD36 via regulating miR-31/MyD88 axis could decrease injury in LPS-irritated MRC-5 cells.	[17]
Pneumonia	Circ_ZNF652 (Up)	-	WI-38	IL-6/8, IL-1β, TNF-α, IκBα, NF-κB p65, Cox-2	miR-181a, JNK, Bax, Bcl-2, Caspase-3/9,	Knockdown of circ_ZNF652 via upregulating miR-181a and inactivating NF-κB and JNK/p38 pathways could decrease injury in LPS-triggered WI-3 cells.	[36]
Particulate Matter ($PM_{2.5}$)-Induced Airway Inflammation	Circ_406961 (-)	-	BEAS-2B, U937, BEBM	IL-6, IL-8	ILF2, IGF2BP1/ 2/3, JAK/STAT	circ_406961 by interacting with ILF2 via activating the STAT3/JNK pathway could regulate $PM_{2.5}$-induced inflammatory response.	[25]
Particulate Matter ($PM_{2.5}$)-induced Airway Inflammation	Circ_TXNRD1 (-)	-	HBECs	IL-6	miR-892a, COX-2	Circ_TXNRD1 by regulating the miR-892a/COX-2 axis could promote PM-induced inflammation.	[54]
Particulate Matter ($PM_{2.5}$)-Induced Airway Inflammation	Circ_Bbs9 (Up)	ICR Mice	RAW264.7	IL-1β, IL-18, TNF-α, NLRP3	miR-30e-5p, Caspase-1	circ_Bbs9 via NLRP3 inflammasome activation could promote PM2.5-induced lung inflammation in mice.	[40]
Acute Lung Injury (ALI)	circ_0054633 (Up)	Male SD Rats	MPVECs	IL-17A, TNF-α, NF-κB p65	-	Knockdown of circ_0054633 could alleviate the inflammation in the LPS-induced ALI model via regulation of NF-κB signaling.	[65]

Table 6
Impact of circRNAs in gastrointestinal disorders.

Disease	Circular RNA	Human/Animal Study	Cell Culture	Inflammatory-Related Targets	Targets & Pathways	Observation	Refs.
Inflammatory Bowel Disease (IBD)	55 up-regulated and 47 downregulated circRNAs	C57BL/6 mice	-	IL-6, TNF-α	miR-6914–5p, Atg7	In colon tissue from the mesalazine-treated mouse with IBD, the profiling of circRNA expression showed a number of important circRNA-miRNA-mRNA pathways that could be involved in IBD action.	[78]
IBD	Circular CDKN2B-AS1 (Down)	ulcerative colitis (UC) samples (n = 17), normal samples (n = 19)	Caco-2	-	HPRT1, p15	Circular RNA CDKN2B-AS1 is associated with IBD.	[44]
IBD	CircRNA_103516 (Up)	Blood samples of Crohn's disease (CD) (n = 90), ulcerative colitis (UC) (n = 90), control (n = 80),	PBMCs	TNF-α, IFN-γ, IL-10	miR-19b-1–5p	circRNA_103516 by sponging miR-19b could participate in molecular mechanism of CD.	[70]
Radiation-Induced Liver Disease (RILD)	Circ_RSF1 (Up)	-	LX2	IL-1β, IL-6, TNF-α, NF-κB p65	miR-146a-5p, Bcl-2, α-SMA, coll-I, RAC1, JAK, SMAD2	Circ_RSF1 by modulating miR-146a-5p could promote inflammatory and fibrotic phenotypes in hepatic stellate cells irradiated with Gy X-ray.	[8]
Anti-Tuberculosis Drug-Induced Liver Injury (ADLI)	hsa_circ_0093884 (Down)	Peripheral blood samples of TB patients (n = 150)	HL-7702	NLRP3, IL-1β	SIRT1, RPS3, Caspase-1	Hsa_circ_0093884 by binding to RPS3 and activating SIRT1 could decrease hepatocyte inflammation in ADLI.	[68]

Moreover, circRNA PVT1 incraeses ischemia-reperfusion injury through modulating expressions of miR-125b and miR-200a [37]. Finally, circ-RELL1 has been found to regulate inflammatory responses through modulation of miR-6873–3p/MyD88/NF-κB axis [23].

2.8. Nervous system disorders

Spinal cord injury is the mostly assessed nervous system disorder in association with circRNAs expression. For instance, circRNA_2960 has been found to stimulate cell apoptosis and increase the inflammatory responses at the site of lesion through sponging miR-124 [56]. Circ_Plek is another circRNA that increases fibrogenic activation in this condition through regulation of miR-135b-5p/TGF-βR1 axis [56]. On the other hand, Circ_014301 can inhibit development of this type of injury via targeting inflammation factors [62]. The impact of circRNAs in the regulation of inflammatory responses in Alzheimer's disease and acute ischemic stroke has been investigated by few studies (Table 8).

2.9. circRNAs and cancer immune response

Assessment of expression of circRNAs that are dysregulated in Alzheimer's disease in a panel of diverse cancer types has shown that circRNAs related with diagnosis and clinical severity of Alzheimer's disease are negatively correlated in more cancer types. Moreover, circRNA-regulated genes have been found to be associated with IL-12-mediated signaling and viral response. Three circRNAs, namely

Table 7
Impact of circRNAs in cardiovascular disorders.

Disease	Circular RNA	Human/Animal Study	Cell Culture	Inflammatory-Related Targets	Targets & Pathways	Observation	Refs.
Myocarditis (MC)	Circ_ACSL1 or (hsa_circ_0071542) (Up)	peripheral bloodsamples: MC (n = 2 and normal samples (n = 20)	AC16	IL-1β, IL-6, TNF-α	miR-8055, MAPK14, cTnT, CKMB, BNP	Circ_ACSL1 by sponging miR-8055 and regulating MAPK14 could aggravate myocardial injury and inflammation.	[75]
Myocardial I/R Injury	Circ_0050908 (Up)	-	HCMs	TRAF3, IL-1β, IL-6, TNF-α	miR-324–5p, Bax, Bcl-2	Knockdown of circ_0050908 could rescue I/R-induced inflammation and oxidative stress.	[27]
Myocardial Infarction (MI)	Circ_MAT2B (Up)	-	H9c2	IL-6, IL-1β, TNF-α	miR-133, PI3K/AKT, Raf/MEK/ERK	Knockdown of circ_MAT2B via up-regulating miR-133 could decrease OGD-induced inflammation in H9c2 cells.	[23]
MI	Circ_PVT1 (Up)	BALB/c mice	Ventricular cardiomyocyte (VC)	TRAF6	miR-125b, miR-200a, SIRT7, Keap1, Nrf2, p53	Knockdown of circ-PVT1 by targeting miR-125b and miR-200a could prevent I/R injury and inflammation.	[37]
Atherosclerotic Cardiovascular Disease (ASCVD)	Circ_RELL1 or (hsa_circ_0002194), (Up)	-	HUVECs, 293T	NF-kB p65	miR-6873–3p, MyD88, ICAM1, VCAM1	In endothelial cells, circ-RELL1 via the miR-6873–3p/MyD88/NF-kB axis could regulate the inflammatory response.	[23]
Abdominal Aortic Aneurysm (AAA)	Circ_Cdyl (-)	C57BL/6J mice, ApoE$^{-/-}$ mice, human aortic samples	RAW264.7, EC, AoSMC, THP-1	TNF-α, MCP1, IL-6	let-7c, C/EBP-δ, IRF4	circ_Cdyl by inducing M1 macrophage polarization and M1-type inflammation could promote AAA formation.	[51]

Table 8
Impact of circRNAs in nervous system disorder.

Disease	Circular RNA	Human/Animal Study	Cell Culture	Inflammatory-Related Targets	Targets & Pathways	Observation	Refs.
Alzheimer's Disease (AD)	Circ_0000950 (Down)	SD Rats	PC12, 293T	IL-6, IL-1β, TNF-α	miR-103, PTGS2, Caspase-3, Bcl-2	Circ_0000950 via sponging miR-103 could increase the level of inflammatory cytokines in AD.	[66]
Acute Ischemic Stroke (AIS)	Circ_HECTD1 (Up)	Peripheral blood samples: AIS (n = 160), normal (n = 160)	-	IL-6, IL-8, IL-10, IL-17, IL-22, IL-1β, TNF-α	-	Higher expression of circ_HECTD1 is correlated with inflammation and recurrence of AIS.	[41]
AIS	Circ_DLGAP4 (Down)	Blood samples AIS (n = 170), control (n = 170)	PBMCs	IL-6/8/17/22, TNF-α, IL-1β	miR-143	Circ-DLGAP4 is negatively correlated with inflammatory cytokine expression in AIS.	[81]
Spinal Cord Injury (SCI)	circRNA-2960 (Up)	SD Rats	-	IL-6, TNF-α, IFN-γ	miR-124	circRNA_2960 by sponging miR-124 could induce apoptosis and elevate the inflammatory response at the lesion site of SCI.	[56]
SCI	Circ_Plek (-)	C57BL/6 mice	Primary spinal fibroblasts	TNF-α	miR-135b-5p, TGF-βR1, Smad	After SCI, circ_Plek by regulating the miR-135b-5p/TGF-βR1 axis increases fibrogenic activation and may be involved in inflammation.	[56]
SCI	Circ_014301 (-)	-	PC12	IL-6, IL-1β, TNF-α, NF-κB	Bax, Bcl-2, Caspase-3	Circ_014301 via targeting inflammation factors could inhibit the development of SCI.	[62]
SCI	Circ_Prkcsh (Up)	C57BL/6 mice, SCI tissue samples (n = 5)	M1800–57	IL-1β, IL-10	miR-488, CCL2, Ago2	Circ_Prkcsh via targeting miR-488 could modulate inflammation factors in SCI.	[6]
Intervertebral DiscDegeneration (IVDD)	Circ_0004354, Circ_0040039 (Up)	IVDD (n = 30), normal tissues (n = 16) from patients with scoliosis	Nucleus pulposus cells (NPCs)	IL-1β	miR-345–3p, FAF1, TP73, Aggrecan, Collagen-II	Circ-RNAs via targeting the miR-345–3p-FAF1/TP73 axis could induce inflammatory response and death in NPC cells in IVDD.	[31]
Neuropathic pain (NP)	Circ_SMEK1 (Up)	SD rats	HAPI	IL-6, IL-1β, TNF-α	miR-216a-5p, TXNIP	Circ_SMEK1 via targeting miR-216a-5p to mediate the expression of TXNIP could increase NP in rats.	[63]

circPICALM, circRTN4 and circMAN2A1 have been found to be the hub nodes in the circRNA/miRNA/target network. Taken together, inflammation signaling regulated by circRNAs is a shared pathogenic process between cancer and Alzheimer's disease [5].

Besides, circRNAs have been shown to modulate the process of inflammation-associated carcinogenesis or tumor-related inflammatory responses, and influence the interaction between tumor microenvironment and the inflammatory cells [42].

2.10. Other disorders

CircRNAs are also involved in the pathophysiology of recurrent spontaneous abortion, periodontitis, diabetes mellitus and its complications, psoriasis and a number of other diseases through modulation of

immune response (Table 9). For instance, knockdown of circ_PUM1 has led to enhancement of proinflammatory factor secretion in trophoblast cells through modulation of miR-30a-5p/JUNB axis [34], thus this circRNA might be involved in the pathogenesis of recurrent spontaneous abortion. In addition, downregulation of hsa_circ_0068087 could ameliorate endothelial cell dysfunction via the TLR4/NF-κB/NLRP3 axis, thus influencing diabetes-related complications [9]. Moreover, circ_0039411 via sponging miR-93–5p could be involved in Nd2O3-induced Inflammation in 16HBE cells [22].

3. Discussion

CircRNAs have been reported to affect pathogenesis of immune-related conditions. CircRNAs have functions such as protein coding and regulation of gene transcription. However, the mostly appreciated route of action of circRNAs is sponging miRNAs. Circ_Ttc3/miR-148a, circ_TLK1/miR-106a-5p, circ_VMA21/miR-9–3p, circ_0068,888/miR-21–5p, circ_VMA21/miR-199a-5p, circ_GRN/miR-214–3p, circ_0003204/miR-491 5p, circ_AFF2/miR-375, circ_0008360/miR-

Table 9
Impact of circRNAs in other disorders.

Disease	Circular RNA	Human/Animal Study	Cell Culture	Inflammatory-Related Targets	Targets & Pathways	Observation	Refs.
Recurrent Spontaneous Abortion (RSA)	Circ_PUM1 (Down)	30 pairs of RSA patients and healthy pregnant women	HTR-8/SVneo	IL-6, IL-8, TNF-α	miR-30a-5p, JUNB, Caspase-3	Knockdown of Circ_PUM1 via the miR-30a-5p/JUNB axis could increase proinflammatory factor secretion in trophoblast cells.	[34]
Periodontitis	Circ_0138959 (Up)	35 periodontitispatients, 30 healthyindividuals	PDLCs	TRAF6	miR-495–3p, RUNX2	Downregulation of circ_0138959 via the miR-495–3p/TRAF6 axis could promote inflammation and attenuate LPS-induced inhibition of proliferation and wound healing.	[10]
Porphyromonas Gingivalis (Pg)-induced complications	Circ-PPP1CC (-)	-	VSMCs	IL-1β, IL-18, TLR9	miR-103a-3p, miR-107, HMGB1, Caspase-1, AIM2	Circ-PPP1CC by activating the HMGB1/TLR9/AIM2 could promote Pg-LPS induced pyroptosis of VSMCs.	[34]
Diabetes mellitus (DM)	hsa_circ_0068087 (Up)	-	HUVECs	TNF-α, IL-6, IL-1β, MCP-1, TLR4, NF-κB, NLRP3	miR-197	Downregulation of hsa_circ_0068087 could ameliorate endothelial cell dysfunction via the TLR4/NF-κB/NLRP3 axis.	[9]
Type 1 Diabetes Mellitus (T1DM)	Circ_PPM1F (Up)	C57BL/6 mice, PBMCs from T1DM (n = 4) and healthy controls (n = 4)	PBMCs, THP1, MIN6, Raw264.7	IL-6, IL-1β, TNF-α, CXCL10, NF-κB p65	HuR, PPM1F, EIF4A3, Bax, Bcl-2, ERK1/2, JNK, mTOR, STAT3, p38	Circ_PPM1F via the HuR/PPM1F/NF-κB axis could modulate M1 macrophage activation and increase pancreatic islet injury and inflammation in T1DM in children.	[28]
Diabetic Retinopathy (DR)	Circ_ZNF532 (Up)	DR (n = 23) and control (n = 23)	hRMECs	IL-6, IL-1β, TNF-α	miR-1243, CARM1	Circ-ZNF532 via targeting the miR-1243/CARM1 axis could facilitate inflammation in DR.	[55]
Essential Hypertension (EH)	hsa_circ_0105015 (Up)	Blood samples: EH (n = 5) and non-EH (n = 5)	HUVECs	-	hsa-miR-637	hsa_circ_0105015 could be associated with EH involved in inflammatory pathways.	[19]
LPS-induced inflammation	Circ_NFIC (-)	-	HD11	IL-1β, TNFα, IFNγ	miR-30e-3p, Caspase-3/8, DENND1B,	Circ_NFIC by regulating DENND1B and sponging miR-30e-3p could balance both apoptosis and inflammation.	[74]
Cytotoxicity induced by neodymium oxide (Nd_2O_3)	Circ_0039411 (Up)	-	16HBE	IL-6, IL-8,	miR-93–5p, MMP2, STAT3	Circ_0039411 via sponging miR-93–5p could be involved in Nd_2O_3-induced Inflammation in 16HBE cells.	[22]
Psoriasis	Circ_OAS3 (Up)	Psoriatic samples (n = 7), normal samples (n = 10)	NHEKs, HaCaT, Ker-CT	IL-6, NF-κB	Hsc70, JNK, STAT3, Cyclin-D1,	Circ_OAS3 by Interacting with Hsc70 via the JNK/STAT3/NF-κB axis could regulate psoriatic inflammation.	[69]
Cryptosporidium Infection	ciRS-7 (Up)	-	HCT-8	NF-κB	miR-1270, RELA, hsp70	ciRS-7 by affecting NF-κB and regulating the miR-1270/RELA axis could increase cyptosporidium parvum propagation.	[34]
Adipose Inflammation (AI)	Circ-ARF3 (-)	C57BL/6J mice	-	TRAF3, IL-6, IL-1β, NLRP3	miR-103, ATG7, caspase-1 MCP-1, Beclin1, LC3-I/II	Circ-ARF3 by targeting the miR-103/TRAF3 axis could alleviate mitophagy-mediated inflammation in mouse adipose tissue.	[26]
Breast Cancer (BCa)	Hsa_circ_0000515 (Up)	BCa (n = 340) and normal (n = 90); Kunming nude mice	MCF-10A, MDA-MB-231, SUM-159, MCF-7, SK-BR-3, MDA-MB-157	TNF-α, COX-2	miR-296–5p, CXCL10, Cyclin-D1, VEGF, MMp-2/9, CRP	Hsa_circ_0000515 via regulating the miR-296–5p/CXCL10 axis is implicated in the development of BCa.	[3]
-	Circ_TUBD1 (-)	-	LX-2	IL-1β, IL-6, TNF-α, TLR4, TRAF6, NF-κB	miR-146a-5p, Bcl-2, IRAK1, Caspase-3/9	Circ_TUBD1 via targeting the tlr4 pathway could affect viability and pro-inflammatory cytokine production of LX-2 Cells.	[39]

135b-5p, circ-FBXW7/miR-216a-3p, ciRS-7/miR-7, circ_0128846/miR-127–5p, circ_0134111/miR-515–5p, hsa_circ_0005567/miR-492, circ-ANKRD36/miR-599, circ-SEC24A/miR-142–5p, circ_HIPK3/miR-561 and circ_HIPK3/miR-192 are examples of circRNA/miRNA pairs that contribute in the pathogenesis of immune-related conditions. Since circRNAs have multiple binding sites for miRNAs, they can construct a platform for establishment of a complex regulatory network. Moreover, as each miRNA can be targeted by several circRNAs as well as long non-coding RNAs (lncRNAs), this interaction network has several layers. Therefore, design of novel therapeutic modalities requires understanding different layers of this complicated network.

CircRNAs participating in the pathoetiology of immune-related disorders can affect expression of several inflammatory molecules, such as IL-6, IL-1β, TNF-α and TRAF6. Moreover, they can influence activity of several signaling pathways, particularly NF-κB. Thus, expression of these circRNAs can affect response of patients to therapeutic options that modulate mentioned inflammatory molecules and signaling pathways.

Altered expression of circRNAs in biofluids can be used as biomarkers for detection of immune-related conditions, prediction of their course and anticipation of response of patients to targeted therapies. This is more highlighted by the fact that circRNAs are stable molecules in the peripheral blood and other biofluids, thus can be used in non-invasive methods of biomarker discovery.

Funding

Not applicable.

CRediT authorship contribution statement

SGF wrote the manuscript and revised it. MT and HP designed and supervised the study. HS, BMH and TS collected the data and designed the figures and tables. All authors read and approved the submitted manuscript.

Declaration of Competing Interest

The authors declare they have no conflict of interest.

Data availability

Not applicable

Acknowledgements

The authors would like to thank the clinical Research Development Unit (CRDU) of Loghman Hakim Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran for their support, cooperation and assistance throughout the period of study.

Ethics approval and consent to participant

Not applicable.

Consent of publication

Not applicable.

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