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Review

Implications and theragnostic potentials of circular RNAs in rheumatic diseases

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ABSTRACT

Circular RNAs (circRNAs), a class of non-coding RNAs (ncRNAs), are highly stable and ubiquitous molecules that exhibit tissue-specific expression. Accumulating evidence has shown that aberrant expression of circRNAs can play a role in the pathogenesis of several diseases. Rheumatic diseases are a varied group of autoimmune and inflammatory disorders affecting mainly the musculoskeletal system. Notably, circRNAs, which are essential immune system gene modulators, are strongly linked to the occurrence and progression of autoimmune disorders. Here, we present and discuss the current findings concerning the roles, implications and theragnostic potentials of circRNAs in common rheumatic diseases, including ankylosing spondylitis (AS), osteoarthritis (OA), osteoporosis (OP), rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), Crohn's disease (CD), and gout. This review aims to provide new insights to support the development of novel diagnostic and therapeutic strategies for these disabling diseases.

1. Introduction

Circular RNAs (circRNAs) are a novel subclass of long non-coding RNAs (lncRNAs) that are ubiquitously expressed in a wide range of species, varying from viruses to mammals [1]. In mammals, circRNAs are frequently expressed in a cell-type- or tissue-specific pattern and are primarily located in the cytoplasm [2]. As their name suggests, circRNAs are circular, single-stranded molecules formed by the back-splicing of a pre-mRNA molecule, a highly regulated process in which the 3′ end of an exon is ligated by a 3′,5′-phosphodiester bond to the 5′ end of the same or an upstream exon [2]. This lack of free 3′ and 5′ ends confers resistance to exoribonucleolytic degradation, rendering circRNAs more stable than their linear counterparts [3].

CircRNAs serve various biological functions; most notably, they act as microRNA (miRNA) "sponges" binding and inhibiting the actions of miRNAs, thus regulating the expression of miRNA target genes [3]. In addition, circRNAs may interact with RNA-binding proteins, acting as i) protein sponges that inhibit protein function, ii) decoys that stabilize proteins, or iii) scaffolds that recruit different proteins to facilitate their interaction [1]. Moreover, circRNAs may modulate transcription, translation, or splicing, and may be involved in regulating multiple biological processes, such as cell proliferation, differentiation, migration, and apoptosis [2]. Despite their classification as lncRNAs, some circRNAs are translated into functional peptides [4].

Abbreviations: AUC, Area Under the Curve; ROC, Receiver Operating Characteristic; KEGG, Kyoto Encyclopedia of Genes and Genomes; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; PMOP, Postmenopausal Osteoporosis; RUNX, Runt-related transcription factor.

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Besides their diverse functions in normal physiology, circRNAs have been implicated in various human diseases, including cardiovascular diseases, autoimmune diseases, neurodegenerative disorders, diabetes, and cancer, highlighting their potential as diagnostic biomarkers and therapeutic targets [5,6]. While some circRNAs have pathological roles, contributing to disease development and progression, other circRNAs may prevent or ameliorate disease by enhancing various physiological functions. For example, *circANRIL* is a circRNA that was found to protect against atherosclerosis by inhibiting proliferation and inducing apoptosis of vascular smooth muscle cells and macrophages [7]. Similarly, *Cdr1as* (*CiRS-7*) was shown to improve pancreatic β-cell function and increase insulin transcription and secretion, through its well-known miRNA-7 sponge activity, indicating its therapeutic potential in diabetes [8]. Some circRNAs act as tumor suppressors and inhibit cancer cell proliferation and migration, such as *circTADA2A-E6*, which inhibits breast cancer progression and metastasis [9]. Conversely, other circRNAs are over-expressed in tumor cells, such as *circPVT1*, which was identified as a proliferative factor in head and neck squamous cell carcinoma and gastric cancer, promoting cell proliferation by acting as a miRNA sponge [10,11]. Furthermore, certain circRNAs have been closely associated with autoimmune disease pathogenesis due to their involvement in immunoregulation and inflammation. [12]. Rheumatic diseases are a diverse group of over 200 autoimmune and inflammatory disorders affecting primarily the musculoskeletal system. While different classifications exist, rheumatic diseases can be classed, based on their nature, as: autoimmune, including rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE); inflammatory, including gout, ankylosing spondylitis (AS), Crohn's disease (CD) and possibly osteoporosis (OP). They can also be classified into metabolic, such as osteoporosis and gout or degenerative, such as osteoarthritis (OA) [13]. Recent studies have identified circRNAs as important players in the development and progression of rheumatic diseases. In this review, we will summarize the accumulating evidence regarding the roles, implications, and theragnostic potentials of circRNAs in some of the common rheumatic diseases, including RA, SLE, OA, AS, OP, CD and gout (Table 1).

2. Ankylosing spondylitis

Ankylosing Spondylitis (AS), a form of spondyloarthritis, is an autoimmune rheumatic disease characterized by chronic inflammation that primarily affects the spinal and sacroiliac joints as well as their adjoining soft tissues, including ligaments and tendons [14]. As the disease progresses, fibrosis and calcification may occur in the spinal joints, causing rigidity and fusion of parts of the spine [15]. Due to its non-specific symptoms, insidious onset, and the lack of specific indicators of early disease, AS diagnosis is frequently delayed by 5 to 10 years [16]. This results in a significant delay in treatment, leading to disability and reduced quality of life [17].

Table 1
CircRNAs as potential diagnostic or prognostic biomarkers for rheumatic diseases.

Disease	CircRNA
Ankylosing spondylitis	hsa_circRNA_102532, hsa_circRNA_001544, hsa_circRNA_012732, hsa_circRNA_008961
Osteoarthritis	hsa_circ_101178, hsa_circRNA_0032131, hsa_circ_0101251, hsa_circ_0104595, hsa_circ_0104873, and hsa_circRNA_0020014
Osteoporosis	circ_0002060, circ_0001275, circ_0076690, hsa_circ_0001445, circ_0006859, circ_0021739
Rheumatoid arthritis	circRNA_0044235, circRNA_104871, ciRS-7, of hsa_circ_0002715, hsa_circ_0035197, circRNA_0005008 and circRNA_0005198, circRNA_0000175, circRNA_0008410, and circRNA_0140271
Systemic lupus erythematosus	circRNA_400011, circRNA_102584, circRNA_101471, circRNA_100226, circRNA_407176, circRNA_001308, circRNA_0057762, circRNA_0003090, circIBTK, circRNA_100236, circRNA_102489, circRNA_101413, circPTPN22, circRNA_0044235, circRNA_0000479, circRNA _0082688, circRNA_0082689, circRNA_0012919, and circHLA-C
Crohn's disease	circRNA_103516, hsa_circRNA_004662, hsa_circRNA_092520, hsa_circRNA_102610, hsa_circRNA_103124, hsa_circRNA_0062142, and hsa_circRNA_0001666
Gout	hsa_circRNA_103657

2.1. The role of circRNAs in the pathogenesis of AS

In an effort to improve its diagnosis and treatment, several studies have investigated the involvement and theragnostic potential of circRNAs in AS. Tang et al. [17] found 1369 differentially expressed circRNAs in AS patients' peripheral blood mononuclear cells (PBMCs), which may be implicated in the disease pathogenesis. Of these, 675 were upregulated and 694 were downregulated in AS patients compared to healthy controls (HCs). Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway analysis indicated that the upregulated circRNAs were mainly involved in inflammatory pathways, such as tumor necrosis factor alpha (TNF-a) and mitogen-activated protein kinase (MAPK) signaling pathways, suggesting their role in AS pathogenesis. On the other hand, the downregulated circRNAs were primarily associated with cancer-related pathways, indicating that similar processes may be involved in the development of AS and certain types of cancer. In the same study, four upregulated circRNAs (predicted to be implicated in AS development through their miRNA sponge activity) were subjected to further analysis [17]. Hsa_circRNA_102532 and hsa_circRNA_001544, which were significantly overexpressed in AS patients compared to HCs, were identified as potential diagnostic markers by plotting receiver operating characteristic (ROC) curves which demonstrated their diagnostic power. Moreover, hsa_circRNA_012732 was reported as a potential prognostic marker, indicator of disease activity, and therapeutic target due to the negative correlation of its expression level with the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), the Bath Ankylosing Spondylitis Functional Index (BASFI), and high-sensitivity C-reactive protein (hsCRP) level. This circRNA was proposed to function as a proinflammatory mediator in AS, contributing to disease progression. Similarly, it was suggested that hsa_circRNA_008961 may serve as an indicator of disease activity as its expression level negatively correlated with platelet count (Table 1).

Using high-throughput RNA sequencing, Zhang et al. identified 56 circRNAs that were differentially expressed (half were upregulated and half were downregulated) in the plasma exosomes (extracellular vesicles containing lipids, proteins, and nucleic acids, secreted by most cells into body fluids) of AS patients compared to HCs [18]. Gene Ontology (GO) analysis revealed that the downregulated circRNAs were involved in negatively regulating the activity of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), an important transcription factor that plays a key role in modulating inflammatory and immune responses [19]. On the other hand, the upregulated circRNAs were suggested to function as regulators of bone remodeling, a hallmark of AS pathophysiological development. Consistent with the knowledge that circRNAs act as miRNA and protein sponges, the GO analysis indicated that the differentially expressed exosomal circRNAs functioned in RNA and protein binding. Moreover, the upregulated circRNAs were proposed to bind Ras-related nuclear protein (Ran), a member of the small GTPases Ras superfamily, which may play a role in AS pathogenesis. KEGG pathway analysis identified the Notch pathway as a major signaling pathway in which the differentially expressed circRNAs participated, highlighting this pathway's targeting as a potential novel treatment strategy for AS. In addition, this analysis indicated that the circRNAs may be involved in immunological processes, such as viral carcinogenesis and human T-cell leukemia virus type 1 (HTLV-1) infection. Furthermore, Zhang et al. selected 5 significantly downregulated exosomal circRNAs (hsa_circ_0110797, hsa_circ_0097378,

hsa_circ_0122309, hsa_circ_0058275, and hsa_circ_0008346) and confirmed their expression by quantitative polymerase chain reaction (qPCR) [18]. Subsequently, a circRNA-miRNA-mRNA interaction network was constructed by determining the top 5 miRNAs targeted by each of the 5 circRNAs, as well as the top 5 mRNAs targeted by each miRNA. Consequently, these 5 circRNAs were suggested to be closely associated with AS, although further research is needed to delineate their exact mechanisms and establish their theragnostic potential [18].

Likewise, Kou et al. identified 123 significantly differentially expressed circRNAs in the spinal ligament tissues of AS patients compared to the expression in patients with lumbar disc herniation (fold change ≥ 1.5, $p < 0.05$), of which 57 were upregulated and 66 were downregulated [20]. GO analysis predicted that these circRNAs mainly participated in regulating peptidyl-serine and peptidyl-threonine phosphorylation and GTPase activity, in addition to binding Ras GTPase. Furthermore, it was predicted that the circRNAs exhibited phosphatidylinositol-3,4,5-triphosphate (PIP_3) binding activity. The results of this analysis suggested that these circRNAs may be implicated in the MAPK and the phosphatidylinositol 3-kinase (PI3K)/protein kinase B (PKB) signaling pathways, which are involved in inflammation-induced chondrocyte apoptosis, which along with GTPases may play a role in AS pathogenesis [20]. Furthermore, KEGG pathway analysis indicated that the differentially expressed circRNAs were also involved in bacterial and viral infections, such as Yersinia, human immunodeficiency virus 1 (HIV-1), and human cytomegalovirus infections, suggesting a role in the immune system modulation [20]. It was also predicted that the circRNAs may serve a function in T cell receptor (TCR) signaling and Th17 cell differentiation, which is in line with the previous finding indicating that Th17 cells play a role in AS pathogenesis by releasing various cytokines causing bone erosion and inflammation [21]. Finally, bioinformatics analysis predicted that 60 of the 123 circRNAs interacted with 221 miRNAs. In particular, hsa_circNFATC1001, hsa_circMNT002, and hsa_circRUSC2002 were predicted to bind 22, 24, and 45 miRNAs, respectively, indicating a potential role of the miRNA sponge activity of these circRNAs in AS development [21].

Consistent with the previous findings, Wang et al. identified 2942 differentially expressed circRNAs in platelets of AS patients relative to HCs, of which 2616 were downregulated and 326 upregulated [22]. GO and KEGG pathway analyses of the 326 upregulated circRNAs predicted their involvement in several functions including platelet degranulation, aggregation, and activation, cell migration, cell-cell adhesion, focal adhesion, extracellular matrix (ECM)-receptor interactions, protein and enzyme binding, protein phosphorylation, human cytomegalovirus infection, and Fc gamma receptor-mediated phagocytosis [22]. These functional enrichment analyses also suggested that the upregulated circRNAs participated in various signaling pathways, including transforming growth factor-beta (TGF-β) receptor, PI3K-PKB, mTOR, cAMP, ErbB, Rap1, and FoxO signaling pathways. These results indicated that the overexpressed circRNAs may play a role in modulating platelet function and chronic inflammation associated with AS [22]. Further, 2 circRNAs, circPTPN22 (hsa_circ_0000110) and circFCHSD2 (hsa_circ_0005918), were found to be downregulated in both the platelets and spinal ligament AS patients tissues, and were predicted to interact with various miRNAs, acting as miRNA sponges that modulate gene expression [22]. These two circRNAs' mRNAs targets were predicted to be mainly associated with Th17 cell differentiation, cell adhesion, inflammatory bowel disease (IBD), cytokine-cytokine receptor interaction, and HTLV-1 infection, as well as with a set of signaling pathways including Jak-STAT, Wnt, and calcium. In this regard, previous studies reported the involvement of Th17 cells, Jak-STAT, and Wnt signaling pathways in AS pathogenesis, *via* participation in bone remodeling, inflammation, immune regulation, as well as in osteoclast and osteoblast proliferation and differentiation [23]. The role of circRNAs in AS pathogenesis opens the door for considering them as potential novel targets for both AS diagnosis and treatment.

Using bioinformatics analysis and *in vitro* cell-based assays, Li et al. elucidated the function of the significantly upregulated circRNA, hsa_circ_0056558, in AS pathogenesis [24]. The study revealed that in AS tissues, hsa_circ_0056558 sponges miRNA-1290 (miR-1290) downregulating its expression while increasing the expression of cyclin-dependent kinase 6 (CDK 6), an important regulator of the cell cycle. This led to the inhibition of cell proliferation and differentiation and the activation of apoptosis, potentially through the PI3K/PKB/NF-κB pathway [24]. These findings further highlight the theragnostic potential of this circRNA.

3. Osteoarthritis

Osteoarthritis (OA), the most common form of arthritis, is characterized by the degeneration of articular cartilage, primarily in the joints of the knees, hips, spine, and hands, causing pain, stiffness, and disability and impairing the quality of life [25]. The disease is particularly prevalent in the elderly and is associated with abnormal functions of chondrocytes, osteoclasts (cells that mediate bone resorption), and ECM [26]. Currently, there is no cure for OA, and treatments are often focused on managing symptoms, especially pain. In addition, current approaches for diagnosing, prognosing, and preventing OA are limited [27]. Thus, novel strategies for the prevention, diagnosis, prognosis, and treatment of OA are needed.

3.1. Differentially expressed circRNAs in OA

Several studies were conducted to investigate the circRNA expression profiles in OA. Li et al. found 42 differentially expressed circRNAs in OA knee joint cartilage [28]. Similarly, Liu et al. determined that 71 circRNAs were expressed differentially in OA articular cartilage, of which 55 were downregulated and 16 were overexpressed [29]. In addition, Xiao et al. 2019 identified 197 circRNAs that were differentially expressed in OA knee condyles [30]. Moreover, Xiang et al. 2019 [31] reported that 122 circRNAs were differentially expressed in OA knee synovia and predicted their involvement in the pathogenesis of OA synovitis. Furthermore, 1380 significantly differentially expressed circRNAs were identified in OA chondrocytes, of which 215 were overexpressed while the remaining were under expressed. Interestingly, some of these circRNAs were found to be associated with OA pathophysiology [32]. Additionally, 17 downregulated and 7 upregulated circRNAs were found in facet joint OA tissues and appear to be involved in the disease pathogenesis [33]. These findings indicate the possible role of differentially expressed circRNAs in OA onset and development.

3.2. Roles of circRNAs in OA pathogenesis and progression

CircRNAs have been associated with the pathogenesis and progression of OA, indicating their potential as molecular targets for OA diagnosis, prognosis, treatment, and prevention [27]. While some circRNAs contribute to the development or progression of OA, others play a protective role against this disease. By sponging their target miRNAs, circRNAs play different roles in various physiological and pathological processes, including chondrocyte apoptosis and proliferation, inflammation, and ECM metabolism (Table 2).

3.2.1. Regulation of chondrocyte apoptosis

Various circRNAs have been demonstrated to play a role in regulating chondrocyte apoptosis, a critical process in OA pathogenesis. One such circRNA is circADAMTS6, which inhibits interleukin-1 β (IL-1β)-induced chondrocyte apoptosis by acting as a sponge for miR-431-5p [34]. Similarly, circANKRD36 prevents IL-1β-mediated chondrocyte apoptosis and inflammation by sponging miR-599 to increase expression of the Castor Zinc Finger 1 (Casz1) transcription factor [35]. Likewise, circ_0092516 binds miR-337-3p to regulate phosphatase and tensin homolog (PTEN) expression, thus inhibiting chondrocytes apoptosis and

Table 2
Roles of circRNAs in the pathogenesis and progression of osteoarthritis.

Biological process	Promotion	Inhibition
Chondrocyte apoptosis	circHIPK3, circ_0136474, circRNA.33186, circ_0114876, circGCN1L1, circ_DHRS3, circCDH13, circRNA-UBE2G1, circRNF121, and circ_0136474, hsa_circ_0037658	circADAMTS6, circANKRD36, circ_0092516, circRNA-9119, ciRS-7, circSERPINE2, circCDK14, hsa_circ_0045714, hsa_circ_0005567
Chondrocyte proliferation	circ_0092516, circCDK14, hsa_circ_0045714	circ_0136474, circRNA.33186, circPSM3, circ_DHRS3
Inflammation	circ_0114876, circRSU1, circGCN1L1, circRNA-MSR, hsa_circ_0005105, circRNA-CDR1as, and circRNA_Atp9b	circANKRD36, ciRS-7
ECM synthesis	circSERPINE2, circPDE4D, circCDK14, hsa_circ_0045714, circ0083429	circCDH13
ECM degradation	circRSU1, circGCN1L1, circ_DHRS3, circTMBIM6, circCDH13, circRNA_100876, circRNA-MSR, hsa_circ_0005105, circRNA_Atp9b, circRNA.33186, circRNA-UBE2G1, circ_0136474, circRNF121, and circRNA-CDR1as, hsa_circ_0037658	circ0083429, ciRS-7
Autophagy	ciRS-7, hsa_circ_0005567	hsa_circ_0037658

promoting their proliferation, resulting in slowed OA progression [36]. Through a similar mechanism, circRNA-9119, a downregulated circRNA in OA cartilage, inhibits IL-1β-induced chondrocyte apoptosis by acting as a miR-26a sponge, resulting in increased PTEN expression [37]. Moreover, ciRS-7, which is downregulated in OA, inhibits chondrocyte apoptosis and inflammation by sponging miR-7 [38]. Further, circSERPINE2, which is also underexpressed in OA cartilage, sponges miR-1271 to inhibit chondrocyte apoptosis and promote ECM anabolism, thereby inhibiting disease progression [39].

Conversely, circHIPK3 expressed at a low level was found to promote OA chondrocyte apoptosis through a sponge activity on miR-124, which reduced SOX8 expression [40]. Similarly, circ_0136474 and circRNA.33186 (upregulated in OA cartilage) enhanced chondrocyte apoptosis and inhibited cell proliferation by sponging miR-127-5p to increase matrix metallopeptidase 13 (MMP13) expression [41,42].

3.2.2. Chondrocyte injury and inflammation

CircRNAs may also contribute to the development of OA by inducing chondrocyte damage and inflammation. For instance, circ_0114876 (overexpressed in OA tissues) promoted IL-1β-induced chondrocyte injury, inflammation, and apoptosis by sponging miR-671, which resulted in regulation of TNF receptor-associated factor 2 (TRAF2) expression [43]. In addition, circRSU1 (overexpressed in OA articular cartilage) promoted OA progression by mediating oxidative stress, consequent inflammation, and ECM degradation, through its miR-93-5p sponge activity which helped regulate mitogen-activated protein kinase kinase (MEK)/extracellular signal–regulated kinase 1/2 (MEK-ERK1/2) and NF-κB signaling [44]. Similarly, by sponging miR-330-3p and increasing TNF-a expression, circGCN1L1 (upregulated in temporomandibular joint osteoarthritis (TMJOA) synoviocytes) promoted synovial inflammation, chondrocyte apoptosis, synoviocyte proliferation, and ECM degradation [45]. Moreover, circPSM3, an overexpressed cirCRNA in OA chondrocytes, was demonstrated to inhibit chondrocyte proliferation and differentiation by sponging miRNA-296-5p [46]. These findings demonstrated circRNAs targeting as a potential novel therapeutic strategy for reducing inflammation and promoting chondrocyte viability and proliferation in OA

3.2.3. Regulation of ECM metabolism

Some circRNAs have been found to regulate chondrocyte ECM homeostasis, thereby facilitating, or delaying OA progression. By sponging miR-103a-3p and thereby regulating fibroblast growth factor 18 (FGF18) expression, circPDE4D promoted the synthesis of ECM proteins, serving a protective role against OA [47]. Similarly, circCDK14 had a protective effect against OA by regulating ECM metabolism, enhancing chondrocyte proliferation, and inhibiting chondrocyte apoptosis, through its miR-125a-5p sponge activity which was shown to suppress the expression of SMAD2 and disrupt the TGF-β signaling pathway that is closely associated with OA pathogenesis [48]. Likewise, hsa_circ_0045714 stimulated ECM synthesis and chondrocyte proliferation, while inhibiting chondrocyte apoptosis, by sponging miR-193b and thereby upregulating insulin-like growth factor 1 receptor, IGF1R [49]. Further, Circ0083429 (downregulated in OA tissues) ameliorated OA by regulating chondrocyte ECM homeostasis, through sponging miR-346 to modulate SMAD3 expression, which in turn regulated the expression of various proteins involved in ECM metabolism, such as the metalloproteinases MMP3, MPP13, and ADAMTS4, as well the ECM proteins aggrecan and type II collagen [50].

On the other hand, circ_DHRS3 (overexpressed in OA cartilage tissue) was found to mediate IL-1β-induced chondrocyte injury, by promoting ECM degradation and chondrocyte apoptosis, and inhibiting chondrocyte proliferation [51]. This was achieved through sponging miR-183-5p, which resulted in increased expression of Gremlin 1, a protein that is involved in OA progression. Similarly, circTMBIM6 (overexpressed in OA cartilage tissue) enhanced chondrocyte ECM degradation in OA by sponging miR-27a, which increased MMP13 expression [52]. Likewise, CircCDH13, an upregulated circRNA in OA chondrocytes, promoted ECM degradation and inhibited its synthesis, in addition to eliciting chondrocyte apoptosis. Thus, CircCDH13 participated in OA pathogenesis, by sponging miR-296-3p to regulate PTEN expression [53]. Moreover, CircRNA_100876, a chondrocyte ECM-related circRNA (circRNA-CER) that is significantly upregulated in OA, was found to mediate ECM degradation by sponging miR-136 to upregulate MMP13 expression [29]. Furthermore, mechanical stress-related circRNA (circRNA-MSR) (overexpressed in damaged OA cartilage) promoted chondrocyte ECM degradation and inflammation by sponging miR-875, resulting in increased TNF-α expression and reduced type II collagen and aggrecan expression [54]. Additionally, by targeting various miRNAs, the circRNAs, hsa_circ_0005105, circRNA_Atp9b, circRNA.33186, circRNA-UBE2G1, circ_0136474, circRNF121, and circRNA-CDR1as, promoted ECM catabolism in OA, in addition to promoting inflammation (hsa_circ_0005105, circRNA-CDR1as, and circRNA_Atp9b) and apoptosis (circRNA-UBE2G1, circRNF121, and circ_0136474) [55,56].

3.2.4. Regulation of autophagy

Autophagy plays a protective role in the early degenerative stage of OA by inhibiting chondrocyte apoptosis [57]. Various circRNAs that mediate or suppress autophagy in OA have been identified. For example, ciRS-7 was reported to promote autophagy and inhibit ECM degradation by sponging miR-7, thereby inhibiting the PI3K/AKT/mTOR signaling pathway [58]. Similarly, hsa_circ_0005567 was shown to inhibit IL-1β-induced chondrocyte apoptosis by inducing autophagy, through its sponge activity on miR-495 which increased the expression of the early autophagy marker ATG14 [59]. On the other hand, hsa_circ_0037658 (overexpressed in OA chondrocytes) inhibited autophagy, thereby suppressing cell growth and promoting apoptosis. Hsa_circ_0037658 knockdown was demonstrated to suppress OA progression by promoting autophagy and inhibiting ECM degradation, suggesting its potential as a novel therapeutic target [60].

3.3. Theragnostic potential of circRNAs in OA

Differentially expressed circRNAs in OA patients could be used as

targets for better diagnosis, prognosis, or treatment of this debilitating disease (Table 1). For example, a positive correlation between serum hsa_circ_101178 levels and OA severity indicated the important role of this upregulated circRNA in OA pathogenesis and its potential as an early diagnostic biomarker for OA [61]. Similarly, hsa_circRNA_0032131, which is implicated in OA development, was identified as a potential diagnostic marker [32]. Moreover, the circRNAs, hsa_circ_0101251, hsa_circ_0104595, and hsa_circ_0104873 (overexpressed in OA synovial fluid) were identified as potential biomarkers for OA diagnosis, as their expression levels were positively correlated with OA severity [62]. Similarly, hsa_circRNA_0020014 in peripheral blood was identified as a potential diagnostic biomarker that could be used to differentiate between OA and Kashin–Beck disease [63].

In addition, the above-mentioned circRNAs that were found to promote or delay OA development or progression may serve as new therapeutic targets. The goal would be to inhibit the expression of circRNAs that promote OA progression and to enhance the expression of circRNAs that delay OA progression. This could pave the road for novel preventive and therapeutic approaches for OA. For instance, Yao et al. 2021 overexpressed Circ0083429 in a mouse model of OA, demonstrating its protective role in OA [50]. Conversely, Zhou et al. 2021b silenced the expression of CircCDH13 in another OA mouse model, considerably ameliorating the disease [53]. In addition, inhibiting circGCN1L1 expression alleviated TMJOA in a rat model [45]. Moreover, the circRNA, CDR1as, was found to play a role in maintaining the proliferation and differentiation potential of human umbilical cord mesenchymal stem cells, suggesting the possibility of targeting this circRNA as a novel OA treatment using stem cell therapy to repair damaged cartilage and bone in affected joints [64].

4. Osteoporosis

Osteoporosis (OP) is a systemic metabolic bone disorder associated with reduced bone density, leading to decreased bone strength and increased bone fragility and fracture risk [65]. The disease is often asymptomatic, becoming evident only following unanticipated bone fractures, mostly involving the wrist, hip, and vertebral bones. OP is the most frequent cause of fractures in the elderly and may significantly reduce quality of life and result in disability [66]. Due to the global increase in life expectancy, OP incidence is increasing worldwide among the aging population [65]. Postmenopausal (type I) OP (PMOP), which is more common than senile (type II) OP, occurs due to the decline in estrogen level following menopause, leading to an increase in bone resorption [67]. The current treatment strategies, which involve drug therapy and surgery, are inadequate [68]. Moreover, novel diagnostic strategies for the early detection of OP are needed to enable timely and effective prevention and treatment of this insidious disease.

4.1. Roles of circRNAs in OP

There is increasing evidence for the involvement of circRNAs in the development and progression of OP. Several studies were conducted to analyze the circRNA expression profiles in samples from OP patients, resulting in the identification of multiple dysregulated circRNAs that are implicated in OP [68]. For example, M. Fu et al. 2022 found a total of 516 dysregulated circRNAs in the exosomes isolated from bone marrow mesenchymal stem cells (BMSCs) of PMOP patients, which may serve as targets for PMOP diagnosis or treatment [69]. Similarly, 373 differentially expressed circRNAs were identified in PBMCs of PMOP patients, which may participate in disease pathogenesis and serve as biomarkers for POMP diagnosis and prognosis [70]. Moreover, H. Zhang et al. 2021 identified 398 significantly dysregulated circRNAs in the peripheral blood of male OP patients, which may contribute to disease development through various molecular mechanisms and signaling pathways. By modulating the differentiation, proliferation, and apoptosis of osteoblasts and osteoclasts, circRNAs play important roles in regulating osteogenesis and osteolysis, thereby promoting or inhibiting OP progression [71] (Tables 3 & 4).

4.1.1. CircRNAs involved in the promotion of OP

Circ_28313 was found to promote osteoclast differentiation and thereby mediate bone resorption in an ovariectomy-induced OP mouse model and in bone marrow-derived monocytes or macrophages (BMM) treated by receptor activator of nuclear factor-κB ligand (RANKL) and macrophage colony-stimulating factor (CSF1), which are cytokines required for osteoclast differentiation [72]. By sponging miR-195a, circ_28313 induced CSF1 expression, stimulating osteoclast differentiation. Circ_28313 knockdown inhibited osteoclast differentiation *in vitro* and *in vivo*, highlighting its potential modulation as a therapeutic approach for OP. In addition, circ_0003865 promoted OP development by inhibiting osteogenic differentiation of BMSCs, through its miR-3653-3p sponge activity which induced the expression of growth arrest-specific protein 1 (GAS1) and reduced the expression of osteogenic genes. Treatment of BMSCs with melatonin inhibited the expression of this circRNA, resulting in enhanced BMSC osteoblastic differentiation, thereby indicating its potential utilization as a novel therapeutic intervention for OP [73]. Similarly, circ_0006859 (significantly overexpressed in exosomes of OP patients) inhibited osteoblastic differentiation of BMSCs by sponging miR-431-5p [74]. Moreover, circSLC8A1 promoted OP by sponging miR-516b-5p to upregulate AKAP2 expression in BMSCs [75]. Furthermore, hsa_circ_0001275 (upregulated in OP) was a likely contributor to OP pathogenesis, as its knockdown resulted in the reversal of dexamethasone-mediated growth inhibition of osteoblasts by promoting the miR-377/CDKN1B axis [76].

4.1.2. CircRNAs involved in the prevention of OP

Various circRNAs were found involved in slowing OP progression by inducing osteoblastic differentiation, leading to enhanced bone formation. For instance, circRNA_0016624 (downregulated in PMOP) served a protective role by promoting osteogenic differentiation, through sponging miR-98 to increase bone morphogenetic protein 2 (BMP2) expression [77]. Likewise, circRNA_0048211 (downregulated in BMSCs of PMOP patients) was reported to protect against PMOP by sponging miRNA-93-5p to increase BMP2 expression, inducing bone alkaline phosphatase (ALP) activity and leading to increased bone mineralization capacity [78]. Similarly, hsa_circ_0006393 (localized in BMSCs and downregulated in glucocorticoid-induced OP patients) promoted osteogenesis by sponging miR-145-5p to induce forkhead box O1 (FOXO1) expression, resulting in increased expression of various osteogenic proteins, including BMP2 [79]. Moreover, circ_0076906 (underexpressed in OP bone tissue and sera) delayed OP progression by sponging miR-1305 to upregulate osteoglycin expression and inducing

Table 3
Mechanisms by which circRNAs promote osteogenesis to inhibit the progression of osteoporosis.

Mechanism	CircRNA
Stimulation of osteoblastic differentiation	circRNA_0016624, circ_0076906, circHmbox1, circ_0011269, circ_0026827, circ_0076690, circRNA YAP1 (circ-0024097), circFOXP1, circ_0019693, circ_0006215, circ_0062582, and circ-DAB1
Promotion of matrix mineralization	circ-0008500
Stimulation of BMSC proliferation	circ-DAB1, circ_0001052
Inhibition of osteoclastogenesis	circ_0007059, circHmbox1, circ_0021739
Inhibition of osteoblast apoptosis	circ-Rtn4, circRNA AFF4
Stimulation of osteoblast proliferation	circRNA AFF4
Upregulation of osteogenic genes	circRNA_0048211, hsa_circ_0006393

Table 4
Mechanisms by which circRNAs promote osteolysis, contributing to the pathogenesis of osteoporosis.

Mechanism	CircRNA
Inhibition of osteogenic differentiation	circ_0003865, circ_0006859
Stimulation of osteoclast differentiation	circ_28313
Growth inhibition of osteoblasts	hsa_circ_0001275
Downregulation of osteogenic genes	circ_0003865

mesenchymal stem cells osteogenic differentiation [80]. In addition, circ_0011269, a downregulated circRNA in OP, induced osteogenic differentiation by sponging miR-122 to increase the expression of RUNX2, a critical transcription factor for osteoblastic differentiation [81]. Additionally, circ-0008500 promoted osteoblast matrix mineralization by sponging miR-1301-3p to induce the expression of peptidyl arginine deiminase 4 (PADI4) which stabilized RUNX2 expression [82]. In a similar way, circ_0026827 promoted osteoblastic differentiation of dental pulp stem cells by miR-188-3p sponging which modulated RUNX1 and Beclin1 expression [83]. Comparably, circ_0076690, circRNA YAP1 (circ-0024097), circFOXP1, circ_0019693, circ_0006215, circ_0062582, and circ-DAB1 induced osteoblastic differentiation by targeting various miRNAs and signaling pathways, promoting bone regeneration in OP [84–90]. In addition, circ-DAB1 promoted BMSC proliferation, adding to its therapeutic role in OP [84].

Another mechanism by which circRNAs could prevent OP progression is the regulation of osteoclast differentiation to inhibit bone resorption. For example, circ_0007059 (upregulated in PMOP) suppressed the differentiation of BMSCs into osteoclasts, through sponging miR-378 to reduce BMP2 expression [91]. Likewise, by sponging miRNA-1247-5p, circHmbox1 inhibited TNF-a-induced osteoclast differentiation and promoted osteoblast differentiation, ameliorating ovariectomy-induced OP in mice [92]. Moreover, circ_0021739, a downregulated circRNA in PMOP, inhibited osteoclast differentiation by sponging miR-502-5p [93].

Furthermore, circRNAs could prevent OP by regulating cell apoptosis and proliferation. For example, the protective role of circ-Rtn4 against OP was demonstrated by overexpressing this circRNA in BMSCs. Exosomes isolated from these modified BMSCs suppressed TNF-α-induced cytotoxicity and apoptosis of murine MC3T3-E1 preosteoblasts, through the miR-146a sponge activity of circ-Rtn4, resulting in increased osteoblast viability [94]. In addition, circ_0001052 protected against OP by mediating BMSC proliferation induced by low-level laser irradiation, through its miRNA-124-3p sponge activity [95]. Similarly, circRNA AFF4 inhibited apoptosis and induced proliferation of MC3T3-E1 cells by sponging miR-7223-5p to regulate PI3KR1, thereby promoting fracture healing *in vivo* [96].

4.2. CircRNAs as diagnostic and prognostic biomarkers for OP

Several circRNAs have been recognized for their diagnostic or prognostic value in OP (Table 1). For example, circ_0002060 and circ_0006873 (upregulated in plasma from OP patients) were associated with reduced bone mineral density (BMD), and the former was identified as a potential diagnostic biomarker for OP [97]. Similarly, circ_0001275, an overexpressed circRNA in PBMCs of PMOP patients, was discovered as a potential diagnostic marker for PMOP [98]. In addition, circ_0076690 (downregulated in OP) was identified as a potential diagnostic and prognostic biomarker, as its expression level significantly correlated with BMD and T-score [85]. Moreover, hsa_circ_0001445 (a downregulated circRNA in the plasma of PMOP patients, whose expression is positively associated with T-score) was indicated as a potential marker for PMOP diagnosis [99]. Likewise, circ_0006859 was reported as a potential diagnostic biomarker for OP [74]. Additionally, circ_0021739 was identified as a potential diagnostic biomarker in PBMCs of PMOP patients, as its expression correlated with T-scores [93].

5. Rheumatoid arthritis

Rheumatoid arthritis (RA) is a chronic and debilitating systemic autoimmune disorder with a global prevalence of 1 %. The main features of RA are synovial hyperplasia, joint synovitis, articular cartilage erosion, and systemic immunological and inflammatory symptoms [100,101]. Patients with RA have an improved therapy and survival rate, yet they still suffer from damage in the joint, disability, and severe disease that extremely impact patients' quality of life causing a huge burden of care [102,103]. Recently, evidence has shown that many elements are involved in RA pathogenesis, such as immunological illness, susceptibility genes, and environmental factors [104,105]. Nevertheless, the molecular mechanisms that trigger RA and further its development and progression of are not fully understood.

Early diagnosis and proper therapy can help RA patients improve their clinical symptoms and prognosis to some extent. Currently, RA can be diagnosed based on the classification criteria of American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) and some serological markers, which include rheumatoid factor and anti-cyclic citrullinated peptide antibodies (ACPA) [106]. However, the diagnostic value of these methods is limited since they have low sensitivity and specificity leading to an elevated rate of misdiagnosis and a poor prognosis [107]. Thus, it is crucial to identify novel biomarkers to improve the early diagnosis and clinical outcomes of RA.

5.1. Role of circRNAs in macrophages

Because of the stability and tissue-specific expression of circRNAs [108], several studies have examined their role in RA. Patients with RA have high numbers of activated macrophages that infiltrate the synovial tissues causing damage to joints. However, the number of macrophages was shown to decrease after effective therapy [108]. Yang et al. explored the role of circRNA in macrophages, demonstrating that the presence of circRNA_09505 in macrophages caused exaggerated inflammation and joint erosion [109]. Specifically, *in vitro* study indicated that macrophage proliferation and cell cycle progression were significantly enhanced with overexpressed circRNA_09505, while inhibited with knockdown of circRNA_09505 [109]. Thus, circRNA_09505 was able to enhance macrophage proliferation and progression of cell cycle. Interestingly, *in vivo* study showed that knocking down circRNA_09505 in macrophages attenuated inflammation and erosion of joints in a collagen-induced arthritis mouse model [109]. circRNA_09505 acted as a sponge for miR-6089 and enhanced TNF -α, IL-6, and IL-12 production. Thus, this circRNA could regulate inflammation *via* the miR-6089/AKT1/NF-κB signaling pathway [109].

5.2. Role of circRNAs in RA tissues

Studies have demonstrated that, despite the inhibition of inflammation, damage and loss of cartilage still occurred [110,111]. A study examined the expression of circRNAs in cartilage tissues of RA patients, revealing that the expression of 36 circRNAs were significantly altered in RA patients compared with controls, among which circFADS2 presented the highest altered expression [112]. Furthermore, lipopolysaccharide (LPS)-treated chondrocytes, a known RA model for examining *in vitro* inflammation, demonstrated raised levels of circFADS2 [112]. Further studies found that, by acting as an interceptor of miR-498/mTOR cross-talking, circFADS2 protected LPS-treated chondrocytes against inflammation and apoptosis [112]. Another study delineated the circRNA expression profile in synovial tissues of RA patients, indicating that there were significant variations in the expression of 29 circRNAs [113]. Further loss-of-function and rescue analyses revealed that circ_0001859 aggravated inflammation in SW982 cells, a cell line of human synovial sarcoma commonly utilized to study RA

pathophysiology [114,115]. Specifically, circ_0001859 acted as a sponge of the miR-204/211 family. By silencing circ_0001859, miR-204/211 expression was upregulated, consequently enhancing the suppression of its target, ATF2, inhibiting its function and decreasing the inflammation in SW982 cells [113].

5.3. Role of circRNAs in fibroblast-like synoviocytes

Fibroblast-like synoviocytes (FLSs), the major constituent cells in RA synovial tissues, mediated inflammation and damage to joints by producing inflammatory mediators, such as cathepsins and metalloproteinases [116]. Accordingly, it is important to investigate the functional significance of circRNAs in FLSs of RA patients to provide new insights into disease pathogenesis. Given that the expression of circRNA_0003353 is markedly increased in FLSs from RA patients, its upregulation could be essential for RA development [117]. Further investigations revealed that circRNA_0003353 contributed to RA progression by regulating inflammation and immunity, as well as cell proliferation, migration, invasion, and apoptosis. Consistent with this finding, overexpression of circRNA_0003353 in FLSs of RA patients enhanced cell proliferation, migration, and invasion, inhibited apoptosis, increased the levels of pro-inflammatory cytokines, and reduced the levels of anti-inflammatory cytokines, whereas its knockdown had the opposite effects [117].

5.4. CircRNAs as diagnostic and prognostic biomarkers for RA

Accumulating findings supported the claim that circRNAs in blood could be utilized as biomarkers for RA diagnosis (Table 1). Therefore, many studies were performed to identify the circRNAs expressed in PBMCs from patients with RA. Five circRNAs (circRNA_092516, circRNA_003524, circRNA_103047, circRNA_104871, and circRNA_101873) were significantly elevated in PBMCs of RA patients. CircRNA_104871 exhibited the highest diagnostic value with 83.3 % sensitivity and 68 % specificity [118]. Based on RT-qPCR analysis, circRNA_0044235 expression levels were shown to be significantly decreased in the peripheral blood of 77 RA patients as compared to healthy controls [119]. The ROC curve analysis of circRNA_0044235 displayed 90 % specificity and 61 % sensitivity, suggesting a potential role for circRNA_0044235 as a biomarker for RA in peripheral blood [119]. It is important to note, however, that studies by both Ouyang et al. and Luo et al. revealed that circRNA_0044235 and circRNA_104871 were not correlated with disease activity of RA [118,119].

Circular CDR1 antisense (ciRS-7), one of the most studied circRNA, was reported to act as a sponge for miR-7, demonstrating the ability to suppress its target genes including mTOR. The expression level of ciRS-7 was shown to be significantly elevated in PBMCs of RA patients [120]. The ciRS-7-mediated suppression of miR-7 function could lead to the alleviation of the inhibitory impacts of miR-8 on mTOR gene [120]. Three circRNAs (hsa_circ_0002715, hsa_circ_0001947, hsa_circ_0000367, and hsa_circ_0035197) were significantly elevated in the peripheral blood of 59 new-onset RA patients as compared to healthy controls [121]. Results from ROC curve analysis indicated that a combination of hsa_circ_0002715 and hsa_circ_0035197 could serve as a potential biomarker in the peripheral blood of new-onset RA patients as it could be correlated with the disease activity [121]. More recently, the expression levels of circRNA_0005008 and circRNA_0005198 were confirmed to be significantly increased in plasma from new-onset RA patients. Analysis using ROC curves indicated that circRNA_0005008 and circRNA_0005198 could have important roles as biomarkers in RA diagnosis [122].

Because of intrinsic defects of microarrays, including their inability to reveal un-identified circRNAs [123], the RNA sequencing technique was utilized to examine the circRNAs expression profile in PBMCs of patients with RA. Results indicated the presence of 71 significantly dysregulated circRNAs (30 downregulated and 41 upregulated) including many newly identified candidate circRNAs [124]. Consistent the RNA-sequencing data, results from RT-qPCR indicated that circRNA_0000396 and circRNA_0130438 were downregulated in RA patients as compared to healthy controls [124]. Results from RNA sequencing and RT-qPCR validation showed that the aberrant expression levels of circRNA_0001200, circRNA_0001566, circRNA_0003972, and circRNA_0008360 were consistent with the results from sequencing assays [125].

To improve the specificity and sensitivity of RA diagnosis, a combination of several circRNAs could be more effective and comprehensive in detecting disease than a single circRNA. In PBMCs from RA patients, circRNA_0000175 was significantly reduced while circRNA_0008410 was significantly elevated and the ROC curve analysis indicated that the combined area under curve (AUC) was 0.971 with 93 % specificity and 93 % sensitivity [126]. The expression levels of circRNA_0000175 and circRNA_0008410 correlated with disease activity and severity in patients with RA. The expression of circRNA_0000175 was associated with anti-citrullinated protein antibodies, white blood cell count, neutrophil count and percentage, lymphocyte count and percentage, and neutrophil to lymphocyte ratio. While the expression of circRNA_0008410 was associated with disease duration, tender joint count, and platelet count (PLT) and plateletcrit (PCT) [126]. However, the results of qRT-PCR in Gao et al. study showed that plasma circRNA_0000175 levels were significantly elevated while circRNA_0044235 levels were significantly reduced in new-onset RA patients compared to healthy group [127]. Moreover, plasma circRNA_0000175 expression in new-onset RA patients correlated with PLT, PCT, and platelet large cell ratio (PLR) while plasma circRNA_0044235 expression correlated with swollen joint count, painful joint count, and disease activity [127]. The ROC analysis also suggested that the combination of these circRNAs (0000175 and 0044235) could enhance the diagnostic accuracy for new-onset RA patients [127].

Since RA has more prevalence among female, one study focused on the role and diagnostic value of PBMC circRNA_0140271 in female patients with RA [128]. Based on RNA-sequencing and RT-qPCR assays, the expression of PBMC circRNA_0140271 was markedly elevated in females with RA compared with healthy females [128]. Results from the ROC analysis demonstrated the ability of circRNA_0140271 to distinguish between females with RA and healthy females with a specificity of 1 and a sensitivity of 0.4 [128]. Besides, the AUC of combined circRNA_0140271 and anti-cyclic citrullinated peptide was 0.818 suggesting improved diagnostic accuracy [128]. Functional studies revealed that circRNA_0140271 could act as a sponge for 8 microRNAs and could be involved in RA development through modulating fatty acid metabolism pathways [128]. Overall, circRNA_0140271 could be utilized as a promising diagnostic biomarker for female patients with RA.

6. Systemic lupus erythematosus

Systemic Lupus Erythematosus (SLE) is a chronic autoimmune disease characterized by extreme inflammation affecting multiple organs and the production of autoantibodies [129]. It is believed that this complex disorder is multifactorial resulting from the co-existence of genetic factors and environmental stimuli, and the association of hormonal abnormalities [130]. The SLE pathogenesis involves a complex web of immune cell interactions that include T lymphocytes, B lymphocytes, and other immune cells leading to the production of large amounts of autoantibodies and inflammatory cytokines in addition to immune cell dysfunction [129]. The exact etiology and molecular mechanisms that trigger the disease development are still not fully understood [131]. Also, the early diagnosis and effective treatments have been a challenge. Treatment targets have been largely autoantibodies such as anti-phospholipid and anti-dsDNA antibodies. The symptoms of SLE could intersect with the symptoms of other autoimmune conditions leading misdiagnosis [132]. Hence, the discovery of novel biomarkers

could help in early diagnosis, accurate diagnosis, and better management of SLE clinical manifestations.

6.1. Blood-derived circRNAs in SLE

The identification of circRNA in blood samples including plasma, whole blood, PBMCs, and T cells could improve SLE diagnosis (Table 1). Using microarray analysis, Li et al. explored the expression profile of circRNAs in plasma specimens from SLE patients and identified 207 circRNAs which were differentially expressed between SLE patients and healthy individuals [133]. Four markedly dysregulated circRNAs (circRNA_400011, circRNA_102584, circRNA_101471, and circRNA_100226) were validated by RT-qPCR and their interaction with SLE-associated miRNA targets predicted with bioinformatics tools suggest they could be used as possible biomarkers for SLE diagnosis [133]. Another study revealed that circRNA_407176 and circRNA_001308 were downregulated in both plasma and PBMCs of SLE patients [134]. Data obtained by ROC analysis, indicate that these circRNAs (407176 and 001308) may be able to distinguish SLE patients from healthy individuals and could be a valuable diagnostic tool for this disease [134].

A recent study examined the circRNAs expression profile in whole blood specimens from children with SLE reporting that a total of 348 circRNAs were significantly dysregulated (184 upregulated and 164 downregulated) [135]. ROC curve analysis results indicated that the expression levels of circRNA_0057762 and circRNA_0003090 could be used to differentiate SLE patients from healthy individuals [135]. Moreover, the comprehensive circRNA-miRNA-mRNA network constructed by Li et al. could provide novel insights into the molecular mechanisms of SLE development in children [135]. A study by Zhang et al. focused on circRNA_0049224 and circRNA_0049220 which have been determined to be significantly reduced in PBMCs of SLE patients and were negatively associated with the SLE disease activity index (SLEDAI) score [136]. The two circRNAs expression levels were positively associated with DNMT1 expression, a main factor in DNA methylation, indicating potential roles in SLE pathogenesis [136].

In another study, downregulation of circIBTK expression and upregulation of miR-29b expression were observed in patients with SLE, both were correlated to SLEDAI score, anti-dsDNA titer, and complement C3 levels [137]. Significantly, the potential roles of circIBTK in SLE pathogenesis include provoking DNA demethylation and activating the AKT signaling pathway through binding to miR-29b [137]. Of note, both abnormal DNA methylation and aberrant AKT signaling pathway activation were observed in SLE pathogenesis [138,139]. Thus, circIBTK and miR-29b could be used as biomarkers and therapeutic targets for patients with SLE [137]. Recently, Zheng et al. discovered 182 upregulated and 563 downregulated circRNAs in PBMCs of SLE patients [132]. Using correlation analysis, circRNA_100236, circRNA_102489, and circRNA_101413 were found to be positively associated with anti-dsDNA, thrombocytopenia, and IgG and were also positively linked with the SLEDAI score indicating that these circRNAs could function as biomarkers for SLE diagnosis [132].

Using RNA sequencing to identify dysregulated circRNAs in PBMCs of patients with SLE led to the discovery of circPTPN22, a novel circRNA that could function as a diagnostic and disease severity biomarker of SLE [140]. The downregulated expression of circPTPN22 was negatively linked to the SLEDAI score in SLE patients. The patients under long-term corticosteroid treatment and high SLEDAI score had markedly elevated levels of circPTPN22 expression [140]. Based on microarray analysis, Luo et al. also demonstrated that two circRNAs (circ_0044235 and circ_0068367) were significantly reduced in SLE patients [141]. The level of hsa-miRNA-892a, miRNA target of circRNA_0044235, was significantly elevated suggesting its use as a potential biomarker for SLE diagnosis [141]. Luo et al. also reported that circRNA_0044235 was markedly decreased in peripheral blood from patients with RA indicating that it could act as a diagnostic indicator for RA [119]. circRNA_0000479 is another circRNA that has been found significantly upregulated in PBMCs of patients with SLE compared with HCs [142]. ROC analysis and AUC values significantly indicated the diagnostic potential of circRNA_0000479 in differentiating subjects with SLE from health individuals [142].

Luo and colleagues chose 11 circRNAs based on reports indicating their upregulation in SLE patients and were able to confirm the expression pattern and clinical importance of these circRNAs [143]. Interestingly, the study replicated the increased expression level of PBMCs circRNA_0000479 from patients with SLE and highlighted its diagnostic value in differentiating SLE from other autoimmune diseases [143]. Moreover, it has been reported that the expression of circRNA_0000479 was correlated with C3 levels, WBC, PLT, autoantibodies, and SLEDAI reflecting activity and severity of SLE [143]. The new-onset SLE patients under regular therapy (corticosteroids and immunosuppressive drugs) were also found to have significantly reduced expression of circRNA_0000479 which could indicate the correlation of this circRNA with immunoregulation [143]. The ROC curve analysis of a combination model of circRNA_0000479 and anti-dsDNA revealed it to be more effective in discriminating SLE patients from healthy controls with 86 % sensitivity, 100 % specificity, and 95 % accuracy indicating that this combination could be utilized as a potential biomarker for assessing SLE diagnosis and therapy [143]. Luo et al. also reported significantly increased expression of three selected circRNAs (circRNA _0082688, circRNA_0082689, and circRNA_0008675) in SLE patients [144]. The combination model of circRNA_0082688, circRNA_0082689, and anti-dsDNA was also showed to efficiently differentiate SLE patients from healthy controls with 95 % sensitivity, 100 % specificity, and 98 % accuracy [144]. Collectively, the combination of circRNA and traditional biomarkers might further enhance the diagnosis of SLE.

Interestingly a spontaneous RNase L activation was observed in PBMCs derived from patients with SLE [145]. The observed RNase L activation caused the degradation of the circRNA needed for regular protein kinase R (PKR) activation. The resulting PKR abnormal activation further enhanced type I IFN production *via* eIF2α phosphorylation ultimately contributing to SLE pathogenesis [145]. In addition, endogenous circRNAs tended to form 16–26 bp imperfect RNA duplexes which served as double-stranded RNA (dsRNA) inhibitors for the activated PKR [145]. Overexpression of dsRNA-containing circRNA in PBMCs of SLE patients could attenuate the abnormal activation of PKR indicating a potential diagnostic value for this circRNA in SLE [145].

6.2. T cell-derived circRNAs in SLE

CD4 T helper (Th) cells have a vital role in SLE pathogenesis [146]. A total of 127 differentially expressed circRNAs were reported in T cells from patients with SLE, and further validated the reduced expression of circRNA_0045272. Functional analysis demonstrated that circRNA_0045272 silencing led to promoted early apoptosis and elevated production of IL-2 in activated Jurkat cells [147]. A study revealed 12 upregulated and 2 downregulated circRNAs in CD4+ T cells from SLE patients [148]. The abnormal high expression of three circRNA was validated by RT-qPCR, including circRNA_0012919, circRNA_0006239, and circRNA_0002227. In particular, Hsa_circ_0012919 expression was confirmed to be associated with SLE characters and different between healthy control and SLE patients suggesting its potential use as SLE diagnostic marker. Downregulation of circRNA_0012919 in CD4+ T cells from both inactive and active SLE patients led to an increase in the expression of DNA methyltransferase 1 and a reduction in the expression of CD11a and CD70 [148]. Notably, the increased expression of both CD11a and CD70 on $CD4^+$ T cells in SLE could enhance the production of autoantibodies [149].

6.3. CircRNAs in lupus nephritis

One of the most severe complications of SLE is lupus nephritis (LN),

which could put the patients at risk of kidney failure and premature death. Based on RNA sequencing, a total of 171 circRNAs with dysregulated expression, 142 upregulated and 29 downregulated circRNAs, were found in renal biopsies of LN patients [150]. The circHLA-C was positively correlated with proteinuria, serum creatinine, renal activity index, and crescentic glomeruli after correlations between seven verified circRNAs and clinical characteristics were examined [150]. circHLA-C could play vital roles in LN development by acting as a sponge for miR-150 to control its expression. Of note, in LN patients, the renal miR-150 was negatively associated with circHLA-C [150].

7. Crohn's disease

Crohn's Disease (CD) is a major type of inflammatory bowel disease (IBD) characterized by transmural inflammation affecting parts of the gastrointestinal tract [151]. Patients with CD can present with complications of strictures and fistulas after 10 years, resulting in significant disability and morbidity [151]. Although CD occurrence has been rising, especially in developing countries, its exact etiology is not completely understood [151,152]. Increasing evidence has shown that molecular mechanisms and contributing factors involved in CD pathogenesis are several and include genetic, environmental, gut microbiome, and mucosal immunity [153,154]. CD clinical symptoms and histological characteristics occasionally overlap with ulcerative colitis (UC), another major type of IBD; although they possess distinct genetic, radiographical, clinical, endoscopic, and immunological features [151,152]. At present, biomarkers detected in patients' feces and blood including the antineutrophil cyto-plasmic antibody (ANCA), anti-*Saccharomyces cerevisiae* antibody (ASCA) and fecal calprotectin have restricted value in distinguishing CD from UC [155]. Differential diagnosis can be particularly challenging when the inflammation is restricted to the colon. Around 10 % of these patients with colon inflammation are diagnosed with unclassified IBD [156]. Novel effective diagnostic biomarkers are thus needed to deliver accurate diagnosis, explore better treatments, and get new insights into CD pathogenesis. In thids contex, long noncoding RNAs and circular RNAs are emerging as a new poetential biomarkers and therapeutic [157,158].

7.1. The role of circRNAs in CD pathogenesis

Several studies have been conducted to assess potential correlation between CD and circRNAs. Ye et al. showed that circRNA_103516 was extremely elevated in the active phase of CD as compared to the remission phase and was positively associated with disease progression as assessed by CD activity index, C-reactive protein (CRP) level, Mayo score, and erythrocyte sedimentation rate (ESR) [159]. In CD patients, circRNA_103516 was also positively associated with pro-inflammatory cytokines such as TNF-α and IFN-γ while negatively linked with anti-inflammatory cytokines such as IL-10 suggesting its correlation with activated pro-inflammatory pathways in CD [159]. The diagnostic values of circRNA_103516 in differentiating CD patients from healthy individuals and ulcerative colitis (UC) patients were 71.67 % and 59.41 % respectively [159]. A higher prevalence of circRNA_103516 was detected in patients with stricture and penetrating CD [159]. Furthermore, a negative correlation between circRNA_103516 and hsa-miRNA-19b-1–5p was observed in CD patients indicating that circRNA_103516 could be involved in CD-related molecular mechanisms *via* hsa-miRNA-19b-1–5p sponging [159]. These findings indicate that circRNA_103516 could be considered as a novel biomarker for CD diagnosing (Table 1).

A microarrays study performed on 10 CD patients and 10 controls reported 163 upregulated circRNAs targeting 435 miRNAs and 55 downregulated circRNAs targeting 207 miRNAs. Specifically, the expression of hsa-circRNA-102685 was found highly upregulated in colon biopsy of CD patients indicating a possible role in CD pathogenesis and a putative regulatory role on different miRNAs including hsa-miR-146b-5p, hsa-miR-182-5p and hsa-miR-146a-5p [160]. Interestingly, another study demonstrated that the same miR-146b can improve intestinal inflammation by up-regulating NF-κB, indicating the modulation of its expression as a potentially helpful therapy for treating intestinal inflammation [161] and modulating T regulatory cells and dendritic cells functions [162]. Furthermore, hsa circRNA 102685 was shown to be implicated in CD through the interaction with apoptosis- and chemokine-associated signaling pathways [160], which were reported to contribute to CD pathogenesis [163–165]. Yin et al. demonstrated that 4 circRNAs (092520, 102610, 004662, and 103124) were significantly up-regulated in PBMCs of CD patients as compared with HCs. ROC and AUC analysis indicated interesting values with diagnostic power, suggesting the expression of these 4 circRNAs n PBMCs can be used as potential diagnostic biomarkers of CD [166].

Similarly, Hu et al. showed that hsa_circRNA_0062142 and hsa_circRNA_0001666 were significantly expressed in CD patients as compared to the control and UC groups. Also in this case, ROC data have favorable diagnostic value suggesting that they could be used as biomarkers for CD [157]. Consonant with their potential diagnostic value in CD, hsa_circRNA_0062142 and hsa_circRNA_0001666 appear to be implicated in many CD-associated cellular functions including Th17 cell differentiation, epithelial to mesenchymal transition (EMT), and carcinogenesis [157]. Since fibrosis is a common characteristic of CD, EMT could contribute to pathogenesis of fibrosis in CD patients through the recruitment of activated fibroblasts in the inflamed intestinal tract [167]. While the involvement of Th17 cells in the progression of CD is believed to take place by their dual role of keeping gut hemostasis and eliciting inflammation lesions [168]. Additionally, imbalance between Th17 and Treg cells has been linked to the pathogenesis of CD [169].

8. Gout

Gout is a common type of inflammatory arthritis that is characterized by disturbances in the metabolism of purine with lowered uric acid excretion leading to elevated amounts of uric acid in the blood and chronic deposition of urate crystals in tissues [170]. The main clinical features of gout involve hyperuricemia, tophi, acute arthritis, deformities of joint, presence of stones in urinary tract, and kidney disease. The prevalence and incidence of gout are increasing globally [171], but its pathogenesis is not fully understood yet. Many factors could be implicated in the development of gout such as genetics, immunity, traumatic stress, and eating behaviors [170–172]. Although the increase in the level of uric acid in the serum is a significant risk factor for the development of gout, only 10 % of patients with hyperuricemia are diagnosed with gout [173]. Warning signs for a possible gout diagnosis include joint symptoms and urate crystals in the joint cavity. Serious symptoms can results from deposition of urate crystals in the joint cavity including joint deformities [170]. Patients often experience comorbid conditions including diabetes, hyperlipidemia, hypertension, cerebrovascular disorders, and cardiovascular disorders [170–172]. Identifying specific biomarkers of gout is important for the development of methods that enable early diagnosis and treatment of gout.

8.1. The role of circRNAs in gout pathogenesis

Studies on the role of circRNAs in gout are limited. Genome-wide microarray analysis for circRNA expression in PBMCs of gout patients showed an abnormal expression of circRNAs [174]. Regarding the genomic regions, the most distinctly expressed circRNAs originated from exons and were widely distributed in almost all chromosomes except the Y chromosome [174]. Concerning their differential expression, a microarray analysis indicated that in the gout group 238 circRNAs were upregulated and 41 circRNAs were downregulated [174]. Bioinformatics analyses showed that the differentially expressed circRNAs appear to be involved in gout pathogenesis through their interaction with various signaling pathways including FoxO, apelin and cGMP-PKG pathway [174]. interestingly, hsa_circRNA_103657 and hsa_circRNA_000241

were significantly overexpressed in the gout group as compared with the healthy control group, and hsa_circRNA_103657 AUC value showed significant diagnostic potential in differentiating gout subject from healthy individuals.

Other studies indicated a role for Toll-like receptor and NOD-like receptor signaling pathways in the development of gout inflammation [170,175]. Dysregulation of hsa_circRNA_103657 and hsa_circRNA_000241, which are significantly upregulated in gout patients, could be involved in gout development *via* affecting PI3k-AKT pathway [174]. Similarly, dysregulated PI3k-AKT signaling was shown to impact uric acid metabolism [176]. In addition to the pathways indicated above hsa_circRNA_103657 and hsa_circRNA_000241 could participate in regulating lipid or glucose metabolism in gout patients [174]. Dai et al. concluded that hsa_circRNA_103657 could be used as a diagnostic biomarker for gout with high specificity and specificity (Table 1 and [174]).

9. Conclusion

Rheumatic diseases are debilitating autoimmune and inflammatory diseases that are often chronic, progressive, and painful, resulting in disability and reduced quality of life. Early diagnosis and treatment are essential to slow disease progression. However, current diagnostic and therapeutic approaches for rheumatic diseases are often limited, highlighting the need for novel diagnostic and therapeutic strategies. Due to their high stability, ubiquity, and tissue-specific expression, circRNAs isolated from accessible body fluids have been increasingly investigated for their theragnostic potential in numerous diseases, including rheumatism. Thanks to the recent advances in RNA sequencing technologies and bioinformatics, a growing number of studies have identified the role of dysregulated circRNAs in various rheumatic diseases, including ankylosing spondylitis (AS), rheumatoid arthritis (RA), osteoarthritis (OA), and systemic lupus erythematosus (SLE). Notably, dysregulated circRNAs may serve pathogenic or protective functions in rheumatic diseases, either promoting or preventing disease development and progression, mostly through their miRNA sponging activity.

Bioinformatic analyses revealed that numerous differentially expressed circRNAs in cells or tissues of AS patients were primarily involved in the regulation of inflammation, immunological processes, and bone remodeling, providing new insights into their possible roles in AS pathogenesis. Moreover, one *in vitro* study elucidated the function of hsa_circ_0056558 in AS development, demonstrating that it inhibits cell proliferation and differentiation while promoting apoptosis, through miR-1290 sponging. Regarding OA, multiple *in vitro* and *in vivo* studies identified the involvement of circRNAs in disease pathogenesis and progression, whereby they advance or ameliorate OA by acting as miRNA sponges that regulate various biological processes, including chondrocyte apoptosis, differentiation, and proliferation, as well as autophagy, inflammation, oxidative stress, and ECM metabolism. In addition, several circRNAs, including hsa_circ_101178, hsa_circRNA_0032131, hsa_circ_0101251, hsa_circ_0104595, hsa_circ_0104873, and hsa_circRNA_0020014, were discovered as potential novel diagnostic biomarkers for OA. In OP, dysregulated circRNAs may increase or decrease disease severity by modulating osteogenesis and osteolysis through different mechanisms, such as the regulation of differentiation, proliferation, or apoptosis of osteoclasts, osteoblasts, or BMSCs. Importantly, circ_0002060, circ_0001275, circ_0076690, hsa_circ_0001445, circ_0006859, and circ_0021739 were recognized as potential biomarkers for OP diagnosis.

Recent studies revealed that overexpressed circRNAs in different cells have many implications in RA pathogenesis which include exaggerated inflammation and joint damage in macrophages, increased inflammatory activity in synovial tissue, and regulated cell proliferation, migration, and invasion of FLSs. By ROC analysis, detection of combined circRNAs in blood has been shown to improve the diagnostic accuracy for patients with RA. In SLE, studies have suggested that some abnormally expressed circRNAs in patients with SLE contributed to DNA demethylation and triggered AKT signaling pathway through serving as miRNA sponges. Also, the combination of traditional biomarkers and circRNA has been reported to improve the diagnosis of SLE such as combination of circRNA _0082688, circRNA_0082689, and anti-dsDNA. Given the role of circRNAs as diagnostic biomarkers for CD, circRNA_004662 could be used as a specific biomarker for differentiating CD from UC. Limited studies were conducted about the role of circRNA in gout. Bioinformatics analysis revealed the contribution of several circRNAs in gout through various signaling pathways including the PI3K-AKT pathway.

In conclusion, *in silico*, *in vitro*, and *in vivo* investigations have demonstrated the roles of abnormally expressed circRNAs in rheumatic diseases, highlighting the possibility of targeting such circRNAs to improve the diagnosis and treatment of these diseases. Overexpression of protective circRNAs and the knockdown of pathogenic circRNAs represent novel therapeutic strategies for rheumatism that are worth exploring.

10. Future directions

Although the studies investigating the circRNA expression profiles provided valuable insights regarding the roles of dysregulated circRNAs in rheumatic diseases, most of them were limited by their small sample sizes. Thus, future studies should incorporate larger sample sizes to improve the reliability of the findings. In addition, given the limited number of studies on circRNAs in gout and CD, more studies need to be conducted. It is also important to note that most studies investigating the involvement and theragnostic potential of circRNAs in AS are based on bioinformatics. Therefore, more *in vitro* and *in vivo* investigations are needed to validate the results and further elucidate the mechanisms by which circRNAs contribute to AS pathogenesis and progression. Similarly, further research utilizing cell-based and animal models is crucial to establish the theragnostic potential of circRNAs in rheumatic diseases. Moreover, the clinical utility of circRNAs in diagnosis and therapy needs to be further studied. Furthermore, as virtually all the studies in the literature have focused solely on the function of circRNAs as miRNA sponges, future studies should explore the role of the other circRNA functions in rheumatic diseases. For example, the function of circRNAs as protein sponges or scaffolds may be investigated by studying the circRNA-protein interactions using various methods, such as RNA immunoprecipitation and RNA-protein pull-down assays. Further, studying the function of translatable circRNAs in the development of rheumatism may provide new valuable insights. Hopefully, extensive research in this field will pave the way for the development of novel theragnostic approaches that target circRNAs to facilitate early detection and effective treatment of these disabling diseases.

CRediT authorship contribution statement

Conceptualization, GP; writing—original draft preparation, AAA, HAA, GP; writing—review and editing, RG, AMA, GLR, HZ, HMA; supervision, GP, HZ; funding acquisition, GP.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability statement

The data presented in this study are available in this article.

References

[1] W.-Y. Zhou, Z.-R. Cai, J. Liu, D.-S. Wang, H.-Q. Ju, R.-H. Xu, Circular RNA: metabolism, functions and interactions with proteins, Mol. Cancer (2020) 172.
[2] C.-Y. Yu, H.-C. Kuo, The emerging roles and functions of circular RNAs and their generation, J. Biomed. Sci. 26 (1) (2019) 29.
[3] L. Santer, C. Bär, T. Thum, Circular RNAs: a novel class of functional RNA molecules with a therapeutic perspective, Mol. Ther. (2019) 1350–1363.
[4] J. Greene, A.-M. Baird, L. Brady, M. Lim, S.G. Gray, R. McDermott, S.P. Finn, Circular RNAs: biogenesis, function and role in human diseases, Front. Mol. Biosci. 4 (2017) 38.
[5] L. Verduci, E. Tarcitano, S. Strano, Y. Yarden, G. Blandino, CircRNAs: role in human diseases and potential use as biomarkers, Cell Death Dis. (2021) 468.
[6] R. Giordo, Y.M. Ahmed, H. Allam, S. Abusnana, L. Pappalardo, G.K. Nasrallah, A. A. Mangoni, G. Pintus, EndMT regulation by small RNAs in diabetes-associated fibrotic conditions: potential link with oxidative stress, Front. Cell Dev. Biol. 9 (2021), 683594.
[7] L.M. Holdt, A. Stahringer, K. Sass, G. Pichler, N.A. Kulak, W. Wilfert, A. Kohlmaier, A. Herbst, B.H. Northoff, A. Nicolaou, G. Gäbel, F. Beutner, M. Scholz, J. Thiery, K. Musunuru, K. Krohn, M. Mann, D. Teupser, Circular non-coding RNA ANRIL modulates ribosomal RNA maturation and atherosclerosis in humans, Nat. Commun. (2016) 12429. Nature Publishing Group.
[8] H. Xu, S. Guo, W. Li, P. Yu, The circular RNA Cdr1as, via miR-7 and its targets, regulates insulin transcription and secretion in islet cells, Sci. Rep. (2015) 12453. Nature Publishing Group.
[9] J.-Z. Xu, C.-C. Shao, X.-J. Wang, X. Zhao, J.-Q. Chen, Y.-X. Ouyang, J. Feng, F. Zhang, W.-H. Huang, Q. Ying, C.-F. Chen, X.-L. Wei, H.-Y. Dong, G.-J. Zhang, M. Chen, circTADA2As suppress breast cancer progression and metastasis via targeting miR-203a-3p/SOCS3 axis, Cell Death Dis. (2019) 175. Nature Publishing Group UK.
[10] J. Chen, Y. Li, Q. Zheng, C. Bao, J. He, B. Chen, D. Lyu, B. Zheng, Y. Xu, Z. Long, Y. Zhou, H. Zhu, Y. Wang, X. He, Y. Shi, S. Huang, Circular RNA profile identifies circPVT1 as a proliferative factor and prognostic marker in gastric cancer, Cancer Lett. (2017) 208–219.
[11] L. Verduci, M. Ferraiuolo, A. Sacconi, F. Ganci, J. Vitale, T. Colombo, P. Paci, S. Strano, G. Macino, N. Rajewsky, G. Blandino, The oncogenic role of circPVT1 in head and neck squamous cell carcinoma is mediated through the mutant p53/YAP/TEAD transcription-competent complex, Genome Biol. (2017) 237. BioMed Central.
[12] Z. Zhou, B. Sun, S. Huang, L. Zhao, Roles of circular RNAs in immune regulation and autoimmune diseases, Cell Death Dis. (2019) 503. BioMed Central.
[13] E. Calle, J.A. Gómez-Puerta, Chapter 1 - the spectrum of rheumatic diseases, in: F. Atzeni, I.F. Masala, D. Aletaha, M. Lee, X.B.T.-H.o.S.A.D. Baraliakos (Eds.), Surgery in Rheumatic and Musculoskeletal Disease, Elsevier, 2018, pp. 1–13. Frontiers Media S.A.
[14] C.-W. Chen, J.C.-C. Wei, J. Gu, D. Yu, Editorial: advances in pathogenesis, etiology, and therapies for ankylosing spondylitis, Front. Immunol. 12 (2021), 822582.
[15] W. Zhu, X. He, K. Cheng, L. Zhang, D. Chen, X. Wang, G. Qiu, X. Cao, X. Weng, Ankylosing spondylitis: etiology, pathogenesis, and treatments, Bone Res. (2019) 22. Nature Publishing Group UK.
[16] W.P. Maksymowych, Biomarkers for diagnosis of axial spondyloarthritis, disease activity, prognosis, and prediction of response to therapy, Front. Immunol. (2019) 305. Frontiers Media S.A.
[17] Y.-P. Tang, Q.-B. Zhang, F. Dai, X. Liao, Z.-R. Dong, T. Yi, Y.-F. Qing, Circular RNAs in peripheral blood mononuclear cells from ankylosing spondylitis, Chin. Med. J. (2021) 2573–2582. Lippincott Williams & Wilkins.
[18] L. Zhang, L. Qu, Y. Zhang, Z. Xu, H. Tang, Differential expression of circular RNAs in plasma exosomes from patients with ankylosing spondylitis, Cell Biol. Int. (2022) 649–659.
[19] J. Dąbek, A. Kułach, Z. Gąsior, Nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB): a new potential therapeutic target in atherosclerosis? Pharmacol. Rep. (2010) 778–783.
[20] J. Kou, G. Liu, X. Liu, T. Li, Y. Wei, Y. Sun, T. Wang, Y. Wang, X. Zheng, Profiling and bioinformatics analysis of differentially expressed circRNAs in spinal ligament tissues of patients with ankylosing spondylitis, Biomed. Res. Int. (2020) 7165893. Hindawi.
[21] D. Simone, M.H.Al Mossawi, P. Bowness, Progress in our understanding of the pathogenesis of ankylosing spondylitis, Rheumatology (Oxford, England) (2018) vi4–vi9. Oxford University Press.
[22] T. Wang, S. Meng, P. Chen, L. Wei, C. Liu, D. Tang, D. Liu, Z. Jiang, X. Hong, Comprehensive analysis of differentially expressed mRNA and circRNA in ankylosing spondylitis patients' platelets, Exp. Cell Res. 409 (2021) 112895.
[23] M. Corr, Wnt signaling in ankylosing spondylitis, Clin. Rheumatol. (2014) 759–762.
[24] X. Li, W. Zhou, Z. Li, F. Guan, Hsa_circ_0056558 regulates cyclin-dependent kinase 6 by sponging microRNA-1290 to suppress the proliferation and differentiation in ankylosing spondylitis, Autoimmunity (2021) 114–128.
[25] T. Neogi, The epidemiology and impact of pain in osteoarthritis, Osteoarthr. Cartil. (2013) 1145–1153.
[26] S. Glyn-Jones, A.J.R. Palmer, R. Agricola, A.J. Price, T.L. Vincent, H. Weinans, A. J. Carr, Osteoarthritis, Lancet (London, England) (2015) 376–387.
[27] G. Cao, Y. Pei, P. Li, P. Liu, Y. Deng, Y. Gao, J. Liu, X. Li, New perspectives on the roles of circular RNAs in osteoarthritis development and progression (review), Exp. Ther. Med. (2021) 1471.
[28] H. Li, H.H. Yang, Z.G. Sun, H.B. Tang, J.K. Min, Whole-transcriptome sequencing of knee joint cartilage from osteoarthritis patients, Bone Joint Res. (2019) 290–303.
[29] Q. Liu, X. Zhang, X. Hu, L. Dai, X. Fu, J. Zhang, Y. Ao, Circular RNA related to the chondrocyte ECM regulates MMP13 expression by functioning as a MiR-136 'Sponge' in human cartilage degradation, Sci. Rep. (2016) 22572. Nature Publishing Group.
[30] K. Xiao, Z. Xia, B. Feng, Y. Bian, Y. Fan, Z. Li, Z. Wu, G. Qiu, X. Weng, Circular RNA expression profile of knee condyle in osteoarthritis by illumina HiSeq platform, J. Cell. Biochem. (2019) 17500–17511.
[31] S. Xiang, Z. Li, Y. Bian, X. Weng, RNA sequencing reveals the circular RNA expression profiles of osteoarthritic synovium, J. Cell. Biochem. (2019) 18031–18040.
[32] Y. Wang, C. Wu, F. Zhang, Y. Zhang, Z. Ren, M.J. Lammi, X. Guo, Screening for differentially expressed circular RNAs in the cartilage of osteoarthritis patients for their diagnostic value, Genet. Test. Mol. Biomarkers (2019) 706–716.
[33] C. Chu, W. Chunshuai, C. Jiajia, Z. Jinlong, X. Pengfei, J. Jiawei, C. Zhiming, Transcriptional information revealed differentially expressed circular RNAs in facet joint osteoarthritis, Biochem. Biophys. Res. Commun. (2018) 790–796.
[34] Q. Fu, L. Li, B. Wang, J. Wu, H. Li, Y. Han, D. Xiang, Y. Chen, J. Zhu, CircADAMTS6/miR-431-5p axis regulate interleukin-1β induced chondrocyte apoptosis, J. Gene Med. 23 (2021) e3304.
[35] J.-L. Zhou, S. Deng, H.-S. Fang, X.-J. Du, H. Peng, Q.-J. Hu, Circular RNA circANKRD36 regulates Casz1 by targeting miR-599 to prevent osteoarthritis chondrocyte apoptosis and inflammation, J. Cell. Mol. Med. (2021) 120–131. John Wiley and Sons Inc.
[36] Z. Huang, W. Ma, J. Xiao, X. Dai, W. Ling, CircRNA_0092516 regulates chondrocyte proliferation and apoptosis in osteoarthritis through the miR-337-3p/PTEN axis, J. Biochem. (2021) 467–475.
[37] C. Chen, P. Yin, S. Hu, X. Sun, B. Li, Circular RNA-9119 protects IL-1β-treated chondrocytes from apoptosis in an osteoarthritis cell model by intercepting the microRNA-26a/PTEN axis, Life Sci. 256 (2020) 117924.
[38] X. Zhou, L. Jiang, G. Fan, H. Yang, L. Wu, Y. Huang, N. Xu, J. Li, Role of the ciRS-7/miR-7 axis in the regulation of proliferation, apoptosis and inflammation of chondrocytes induced by IL-1β, Int. Immunopharmacol. (2019) 233–240.
[39] S. Shen, Y. Wu, J. Chen, Z. Xie, K. Huang, G. Wang, Y. Yang, W. Ni, Z. Chen, P. Shi, Y. Ma, S. Fan, CircSERPINE2 protects against osteoarthritis by targeting miR-1271 and ETS-related gene, Ann. Rheum. Dis. (2019) 826–836. BMJ Publishing Group.
[40] Q. Wu, Z.-H. Yuan, X.-B. Ma, X.-H. Tang, Low expression of CircRNA HIPK3 promotes osteoarthritis chondrocyte apoptosis by serving as a sponge of miR-124 to regulate SOX8, Eur. Rev. Med. Pharmacol. Sci. (2020) 7937–7945.
[41] Z. Li, B. Yuan, Z. Pei, K. Zhang, Z. Ding, S. Zhu, Y. Wang, Z. Guan, Y. Cao, Circ_0136474 and MMP-13 suppressed cell proliferation by competitive binding to miR-127-5p in osteoarthritis, J. Cell. Mol. Med. (2019) 6554–6564.
[42] Z.-B. Zhou, G.-X. Huang, Q. Fu, B. Han, J.-J. Lu, A.-M. Chen, L. Zhu, circRNA.33186 contributes to the pathogenesis of osteoarthritis by sponging miR-127-5p, Mol. Ther. (2019) 531–541.
[43] Q. Wang, S. Luo, J. Yang, J. Li, S. Huan, G. She, Z. Zha, Circ_0114876 promoted IL-1β-induced chondrocyte injury by targeting miR-671/TRAF2 axis, Biotechnol. Lett. (2021) 791–802.
[44] Y. Yang, P. Shen, T. Yao, J. Ma, Z. Chen, J. Zhu, Z. Gong, S. Shen, X. Fang, Novel role of circRSU1 in the progression of osteoarthritis by adjusting oxidative stress, Theranostics (2021) 1877–1900. Ivyspring International Publisher.
[45] H. Zhu, Y. Hu, C. Wang, X. Zhang, D. He, CircGCN1L1 promotes synoviocyte proliferation and chondrocyte apoptosis by targeting miR-330-3p and TNF-α in TMJ osteoarthritis, Cell Death Dis. (2020) 284. Nature Publishing Group UK.
[46] J.-L. Ni, X.-Q. Dang, Z.-B. Shi, CircPSM3 inhibits the proliferation and differentiation of OA chondrocytes by targeting miRNA-296-5p, Eur. Rev. Med. Pharmacol. Sci. (2020) 3467–3475.
[47] Y. Wu, Z. Hong, W. Xu, J. Chen, Q. Wang, J. Chen, W. Ni, Z. Mei, Z. Xie, Y. Ma, J. Wang, J. Lu, C. Chen, S. Fan, S. Shen, Circular RNA circPDE4D protects against osteoarthritis by binding to miR-103a-3p and regulating FGF18, Mol. Ther. (2021) 308–323. American Society of Gene & Cell Therapy.
[48] P. Shen, Y. Yang, G. Liu, W. Chen, J. Chen, Q. Wang, H. Gao, S. Fan, S. Shen, X. Zhao, CircCDK14 protects against Osteoarthritis by sponging miR-125a-5p and promoting the expression of Smad2, Theranostics (2020) 9113–9131. Ivyspring International Publisher.
[49] B.-F. Li, Y. Zhang, J. Xiao, F. Wang, M. Li, X.-Z. Guo, H.-B. Xie, H. Xia, B. Chen, Hsa_circ_0045714 regulates chondrocyte proliferation, apoptosis and extracellular matrix synthesis by promoting the expression of miR-193b target gene IGF1R, Hum. Cell (2017) 311–318.
[50] T. Yao, Y. Yang, Z. Xie, Y. Xu, Y. Huang, J. Gao, S. Shen, H. Ye, Y. Iranmanesh, S. Fan, J. Ma, Circ0083429 regulates osteoarthritis progression via the Mir-346/SMAD3 axis, Front. Cell Dev. Biol. (2021) 579945. Frontiers Media S.A.
[51] R. Jiang, H. Gao, F. Cong, W. Zhang, T. Song, Z. Yu, Circ_DHRS3 positively regulates GREM1 expression by competitively targeting miR-183-5p to modulate IL-1β-administered chondrocyte proliferation, apoptosis and ECM degradation, Int. Immunopharmacol. 91 (2021) 107293.

[52] Z.-M. Bai, M.-M. Kang, X.-F. Zhou, D. Wang, CircTMBIM6 promotes osteoarthritis-induced chondrocyte extracellular matrix degradation via miR-27a/MMP13 axis, Eur. Rev. Med. Pharmacol. Sci. (2020) 7927–7936.
[53] Z. Zhou, J. Ma, J. Lu, A. Chen, L. Zhu, Circular RNA CircCDH13 contributes to the pathogenesis of osteoarthritis via CircCDH13/miR-296-3p/PTEN axis, J. Cell. Physiol. (2021) 3521–3535.
[54] Q. Liu, X. Zhang, X. Hu, L. Yuan, J. Cheng, Y. Jiang, Y. Ao, Emerging roles of circRNA related to the mechanical stress in human cartilage degradation of osteoarthritis, Mol. Ther.–Nucleic Acids (2017) 223–230. American Society of Gene & Cell Therapy.
[55] J. Wang, B. Yang, C. Wu, Y. Guo, X. Jiang, Y. Zhang, Role of circular RNAs in osteoarthritis (review), Exp. Ther. Med. (2021) 1279. D.A. Spandidos.
[56] T. Wang, Z. Hao, C. Liu, L. Yuan, L. Li, M. Yin, Q. Li, Z. Qi, Z. Wang, LEF1 mediates osteoarthritis progression through circRNF121/miR-665/MYD88 axis via NF-κB signaling pathway, Cell Death Dis. (2020) 598.
[57] X. Mao, Y. Cao, Z. Guo, L. Wang, C. Xiang, Biological roles and therapeutic potential of circular RNAs in osteoarthritis, Mol. Ther.–Nucleic Acids 24 (2021) 856–867.
[58] X. Zhou, J. Li, Y. Zhou, Z. Yang, H. Yang, D. Li, J. Zhang, Y. Zhang, N. Xu, Y. Huang, L. Jiang, Down-regulated ciRS-7/up-regulated miR-7 axis aggravated cartilage degradation and autophagy defection by PI3K/AKT/mTOR activation mediated by IL-17A in osteoarthritis, Aging (2020) 20163–20183.
[59] J. Zhang, F. Cheng, G. Rong, Z. Tang, B. Gui, Hsa_circ_0005567 activates autophagy and suppresses IL-1β-induced chondrocyte apoptosis by regulating miR-495, Front. Mol. Biosci. (2020) 216. Frontiers Media S.A.
[60] C. Sui, D. Liu, Y. Que, S. Xu, Y. Hu, Knockdown of hsa_circ_0037658 inhibits the progression of osteoarthritis via inducing autophagy, Hum. Cell (2021) 76–85.
[61] C. Chen, Serum hsa_circ_101178 as a potential biomarker for early prediction of osteoarthritis, Clin. Lab. (2020).
[62] F. Yu, C. Xie, J. Sun, H. Feng, X. Huang, Circular RNA expression profiles in synovial fluid: a promising new class of diagnostic biomarkers for osteoarthritis, Int. J. Clin. Exp. Pathol. (2018) 1338–1346, e-Century Publishing Corporation.
[63] Y. Wang, C. Wu, Y. Zhang, Y. Yang, Z. Ren, M.J. Lammi, X. Guo, Screening for differentially expressed circRNA between Kashin-Beck disease and osteoarthritis patients based on circRNA chips, Clin. Chim. Acta (2020) 92–101.
[64] L. Yang, Z. Bin, S. Hui, L. Rong, B. You, P. Wu, X. Han, H. Qian, W. Xu, The role of CDR1as in proliferation and differentiation of human umbilical cord-derived mesenchymal stem cells, Stem Cells Int. (2019) 2316834. Hindawi.
[65] T. Sözen, L. Özışık, N.Ç. Başaran, An overview and management of osteoporosis, Eur. J. Rheumatol. (2017) 46–56. Medical Research and Education Association.
[66] N. Salari, H. Ghasemi, L. Mohammadi, M.H. Behzadi, E. Rabieenia, S. Shohaimi, M. Mohammadi, The global prevalence of osteoporosis in the world: a comprehensive systematic review and meta-analysis, J. Orthop. Surg. Res. (2021) 609. Hindawi.
[67] R. Eastell, T.W. O'Neill, L.C. Hofbauer, B. Langdahl, I.R. Reid, D.T. Gold, S. R. Cummings, Postmenopausal osteoporosis, Nat. Rev. Dis. Primers. (2016) 16069.
[68] W. Chen, B. Zhang, X. Chang, Emerging roles of circular RNAs in osteoporosis, J. Cell. Mol. Med. (2021) 9089–9101. BioMed Central.
[69] M. Fu, L. Fang, X. Xiang, X. Fan, J. Wu, J. Wang, Microarray analysis of circRNAs sequencing profile in exosomes derived from bone marrow mesenchymal stem cells in postmenopausal osteoporosis patients, J. Clin. Lab. Anal. 36 (2022) e23916.
[70] W. Diao, Y. Wang, J. Zhang, H. Shao, Y. Huang, M. Jin, Identification and comparison of novel circular RNAs with associated co-expression and competing endogenous RNA networks in postmenopausal osteoporosis, J. Orthop. Surg. Res. (2021) 459.
[71] H. Zhang, X. Song, Z. Teng, S. Cheng, W. Yu, X. Yao, Z. Song, Y. Zhang, Key circular RNAs identified in male osteoporosis patients by whole transcriptome sequencing, PeerJ 9 (2021) e11420.
[72] X. Chen, Z. Ouyang, Y. Shen, B. Liu, Q. Zhang, L. Wan, Z. Yin, W. Zhu, S. Li, D. Peng, CircRNA_28313/miR-195a/CSF1 axis modulates osteoclast differentiation to affect OVX-induced bone absorption in mice, RNA Biol. (2019) 1249–1262. Taylor & Francis.
[73] X. Wang, T. Chen, Z. Deng, W. Gao, T. Liang, X. Qiu, B. Gao, Z. Wu, J. Qiu, Y. Zhu, Y. Chen, Z. Liang, H. Zhou, C. Xu, A. Liang, P. Su, Y. Peng, D. Huang, Melatonin promotes bone marrow mesenchymal stem cell osteogenic differentiation and prevents osteoporosis development through modulating circ_0003865 that sponges miR-3653-3p, Stem Cell Res Ther (2021) 150. BioMed Central.
[74] F. Zhi, Y. Ding, R. Wang, Y. Yang, K. Luo, F. Hua, Exosomal hsa_circ_0006859 is a potential biomarker for postmenopausal osteoporosis and enhances adipogenic versus osteogenic differentiation in human bone marrow mesenchymal stem cells by sponging miR-431-5p, Stem Cell Res Ther (2021) 157. BioMed Central.
[75] C. Lin, W. Zhong, W. Yan, J. Yang, W. Zheng, Q. Wu, Circ-SLC8A1 regulates osteoporosis through blocking the inhibitory effect of miR-516b-5p on AKAP2 expression, J. Gene Med. 22 (2020) e3263.
[76] Y. Xu, L. Sun, J. Hu, S. Xu, Knockdown of hsa_circ_0001275 reverses dexamethasone-induced osteoblast growth inhibition via mediation of miR-377/CDKN1B axis, Public Library of Science, PloS one (2021). pp. e0252126-e0252126.
[77] L. Yu, Y. Liu, circRNA_0016624 could sponge miR-98 to regulate BMP2 expression in postmenopausal osteoporosis, Biochem. Biophys. Res. Commun. (2019) 546–550.
[78] L. Qiao, C.-G. Li, D. Liu, CircRNA_0048211 protects postmenopausal osteoporosis through targeting miRNA-93-5p to regulate BMP2, Eur. Rev. Med. Pharmacol. Sci. (2020) 3459–3466.
[79] X.-B. Wang, P.-B. Li, S.-F. Guo, Q.-S. Yang, Z.-X. Chen, D. Wang, S.-B. Shi, circRNA_0006393 promotes osteogenesis in glucocorticoid-induced osteoporosis by sponging miR-145-5p and upregulating FOXO1, Mol. Med. Rep. (2019) 2851–2858.
[80] J. Wen, Z. Guan, B. Yu, J. Guo, Y. Shi, L. Hu, Circular RNA hsa_circ_0076906 competes with OGN for miR-1305 biding site to alleviate the progression of osteoporosis, Int. J. Biochem. Cell Biol. 122 (2020) 105719.
[81] X. Xu, Y. Chen, B. Tan, D. Wang, Z. Yuan, F. Wang, Circular RNA circ_0011269 sponges miR-122 to regulate RUNX2 expression and promotes osteoporosis progression, 122, J. Cell. Biochem. (2020) 105719.
[82] Q. Zhai, Y. Zhao, L. Wang, Y. Dai, P. Zhao, X. Xiang, K. Liu, W. Du, W. Tian, B. Yang, T. Li, L. Wang, CircRNA hsa_circ_0008500 acts as a miR-1301-3p sponge to promote osteoblast mineralization by upregulating PADI4, Front. Cell Dev. Biol. 8 (2020) 602731.
[83] F. Ji, L. Zhu, J. Pan, Z. Shen, Z. Yang, J. Wang, X. Bai, Y. Lin, J. Tao, hsa_circ_0026827 promotes osteoblast differentiation of human dental pulp stem cells through the Beclin1 and RUNX1 signaling pathways by sponging miR-188-3p, Front. Cell Dev. Biol. (2020) 470.
[84] W. Chia, J. Liu, Y.-G. Huang, C. Zhang, A circular RNA derived from DAB1 promotes cell proliferation and osteogenic differentiation of BMSCs via RBPJ/DAB1 axis, Cell Death Dis. (2020) 372. Nature Publishing Group UK.
[85] S. Han, M. Kuang, C. Sun, H. Wang, D. Wang, Q. Liu, Circular RNA hsa_circ_0076690 acts as a prognostic biomarker in osteoporosis and regulates osteogenic differentiation of hBMSCs via sponging miR-152, Aging Impact J. (2020) 15011–15020.
[86] Y. Huang, D. Xiao, S. Huang, J. Zhuang, X. Zheng, Y. Chang, D. Yin, Circular RNA YAP1 attenuates osteoporosis through up-regulation of YAP1 and activation of Wnt/β-catenin pathway, Biomed. Pharmacother. 129 (2020) 110365.
[87] W. Shen, B. Sun, C. Zhou, W. Ming, S. Zhang, X. Wu, CircFOXP1/FOXP1 promotes osteogenic differentiation in adipose-derived mesenchymal stem cells and bone regeneration in osteoporosis via miR-33a-5p, J. Cell. Mol. Med. (2020) 12513–12524. John Wiley and Sons Inc.
[88] H. Ji, X. Cui, Y. Yang, X. Zhou, CircRNA hsa_circ_0006215 promotes osteogenic differentiation of BMSCs and enhances osteogenesis-angiogenesis coupling by competitively binding to miR-942-5p and regulating RUNX2 and VEGF, Aging (2021) 10275–10288.
[89] F. Li, H. Wu, G. Zou, D. Cang, Y. Shen, Circular RNA_0062582 promotes osteogenic differentiation of human bone marrow mesenchymal stem cells via regulation of microRNA-145/CBFB axis, Bioengineered (2021) 1952–1963.
[90] W. He, X. Shi, Z. Guo, H. Wang, M. Kang, Z. Lv, Circ_0019693 promotes osteogenic differentiation of bone marrow mesenchymal stem cell and enhances osteogenesis-coupled angiogenesis via regulating microRNA-942-5p-targeted purkinje cell protein 4 in the development of osteoporosis, Bioengineered (2022) 2181–2193. Taylor & Francis.
[91] S. Liu, C. Wang, J. Bai, X. Li, J. Yuan, Z. Shi, N. Mao, Involvement of circRNA_0007059 in the regulation of postmenopausal osteoporosis by promoting the microRNA-378/BMP-2 axis, Cell Biol. Int. (2021) 447–455.
[92] Z. Liu, C. Li, P. Huang, F. Hu, M. Jiang, X. Xu, B. Li, L. Deng, T. Ye, L. Guo, CircHmbox1 targeting miRNA-1247-5p is involved in the regulation of bone metabolism by TNF-α in postmenopausal osteoporosis, Front. Cell Dev. Biol. (2020) 594785. Frontiers Media S.A.
[93] J. Guan, L. Gan, D. Jin, X. Wu, L. Cheng, M. Liu, Y. Fan, J. Zhou, H. Zhang, Y. Zhang, P. Zhou, Overexpression of circ_0021739 in peripheral blood mononuclear cells in women with postmenopausal osteoporosis is associated with reduced expression of microRNA-194-5p in osteoclasts, Med. Sci. Monit. 27 (2021), e929170.
[94] G. Cao, X. Meng, X. Han, J. Li, Exosomes derived from circRNA Rtn4-modified BMSCs attenuate TNF-α-induced cytotoxicity and apoptosis in murine MC3T3-E1 cells by sponging miR-146a, Biosci. Rep. 40 (2020), BSR20193436.
[95] N. Liu, W. Lu, X. Qu, C. Zhu, LLLI promotes BMSC proliferation through circRNA_0001052/miR-124-3p, Lasers Med. Sci. (2022) 849–856.
[96] B. Mi, Y. Xiong, L. Chen, C. Yan, Y. Endo, Y. Liu, J. Liu, L. Hu, Y. Hu, Y. Sun, F. Cao, W. Zhou, G. Liu, CircRNA AFF4 promotes osteoblast cells proliferation and inhibits apoptosis via the Mir-7223-5p/PIK3R1 axis, Aging Impact J. (2019) 11988–12001.
[97] Y. Huang, J. Xie, E. Li, Comprehensive circular RNA profiling reveals circ_0002060 as a potential diagnostic biomarkers for osteoporosis, J. Cell. Biochem. (2019) 15688–15694.
[98] K. Zhao, Q. Zhao, Z. Guo, Z. Chen, Y. Hu, J. Su, L. Chen, Z. He, X. Cai, M. Chen, L. Zheng, W. Wang, Q. Wang, Hsa_Circ_0001275: a potential novel diagnostic biomarker for postmenopausal osteoporosis, Cell. Physiol. Biochem. (2018) 2508–2516.
[99] S. Xiang, Y. Wu, H. Shi, L. Xue, K. Luo, Y. Ding, Circular RNA hsa_circ_0001445 in plasma as a novel biomarker for osteoporosis in postmenopausal women, Biomark. Med (2020) 1599–1607.
[100] D. van der Woude, A.H.M. van der Helm-van Mil, Update on the epidemiology, risk factors, and disease outcomes of rheumatoid arthritis, Best Pract. Res. Clin. Rheumatol. 32 (2) (2018) 174–187.
[101] D. Aletaha, J.S. Smolen, Diagnosis and management of rheumatoid arthritis: a review, JAMA 320 (13) (2018) 1360–1372.
[102] P. Conigliaro, P. Triggianese, E. De Martino, G.L. Fonti, M.S. Chimenti, F. Sunzini, A. Viola, C. Canofari, R. Perricone, Challenges in the treatment of rheumatoid arthritis, Autoimmun. Rev. 18 (7) (2019) 706–713.
[103] G.R. Burmester, J.E. Pope, Novel treatment strategies in rheumatoid arthritis, Lancet 389 (10086) (2017) 2338–2348.

[104] D.J. Veale, C. Orr, U. Fearon, Cellular and molecular perspectives in rheumatoid arthritis, Semin. Immunopathol. 39 (4) (2017) 343–354.
[105] D. Alpízar-Rodríguez, A. Finckh, Environmental factors and hormones in the development of rheumatoid arthritis, Semin. Immunopathol. 39 (4) (2017) 461–468.
[106] D. Aletaha, T. Neogi, A.J. Silman, J. Funovits, D.T. Felson, C.O. Bingham III, N. S. Birnbaum, G.R. Burmester, V.P. Bykerk, M.D. Cohen, B. Combe, K. H. Costenbader, M. Dougados, P. Emery, G. Ferraccioli, J.M. Hazes, K. Hobbs, T. W. Huizinga, A. Kavanaugh, J. Kay, T.K. Kvien, T. Laing, P. Mease, H.A. Ménard, L.W. Moreland, R.L. Naden, T. Pincus, J.S. Smolen, E. Stanislawska-Biernat, D. Symmons, P.P. Tak, K.S. Upchurch, J. Vencovsky, F. Wolfe, G. Hawker, 2010 rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative, Ann. Rheum. Dis. 69 (9) (2010) 1580–1588.
[107] D.M. Boeters, C. Gaujoux-Viala, A. Constantin, A.H.M. van der Helm-van Mil, The 2010 ACR/EULAR criteria are not sufficiently accurate in the early identification of autoantibody-negative rheumatoid arthritis: results from the Leiden-EAC and ESPOIR cohorts, Semin. Arthritis Rheum. 47 (2) (2017) 170–174.
[108] Y. Xu, F. Chen, Current status of functional studies on circular RNAs in rheumatoid arthritis and their potential role as diagnostic biomarkers, J. Inflamm. Res. 14 (2021) 1185–1193.
[109] J. Yang, M. Cheng, B. Gu, J. Wang, S. Yan, D. Xu, CircRNA_09505 aggravates inflammation and joint damage in collagen-induced arthritis mice via miR-6089/AKT1/NF-κB axis, Cell Death Dis. 11 (10) (2020) 833.
[110] H. Rezaei, S. Saevarsdottir, K. Forslind, K. Albertsson, H. Wallin, J. Bratt, S. Ernestam, P. Geborek, I.F. Pettersson, R.F. van Vollenhoven, In early rheumatoid arthritis, patients with a good initial response to methotrexate have excellent 2-year clinical outcomes, but radiological progression is not fully prevented: data from the methotrexate responders population in the SWEFOT trial, Ann. Rheum. Dis. 71 (2) (2012) 186–191.
[111] R.P. Zhou, B.B. Dai, Y.Y. Xie, X.S. Wu, Z.S. Wang, Y. Li, Z.Q. Wang, S.Q. Zu, J. F. Ge, F.H. Chen, Interleukin-1β and tumor necrosis factor-α augment acidosis-induced rat articular chondrocyte apoptosis via nuclear factor-kappaB-dependent upregulation of ASIC1a channel, Biochim. Biophys. Acta Mol. basis Dis. 1864 (1) (2018) 162–177.
[112] G. Li, W. Tan, Y. Fang, X. Wu, W. Zhou, C. Zhang, Y. Zhang, Y. Liu, G. Jiu, D. Liu, circFADS2 protects LPS-treated chondrocytes from apoptosis acting as an interceptor of miR-498/mTOR cross-talking, Aging (Albany NY) 11 (10) (2019) 3348–3361.
[113] B. Li, N. Li, L. Zhang, K. Li, Y. Xie, M. Xue, Z. Zheng, Hsa_circ_0001859 regulates ATF2 expression by functioning as an MiR-204/211 sponge in human rheumatoid arthritis, J Immunol Res 2018 (2018), 9412387.
[114] T. Yamazaki, T. Yokoyama, H. Akatsu, T. Tukiyama, T. Tokiwa, Phenotypic characterization of a human synovial sarcoma cell line, SW982, and its response to dexamethasone, In Vitro Cell. Dev. Biol. Anim. 39 (8–9) (2003) 337–339.
[115] J.H. Chang, K.J. Lee, S.K. Kim, D.H. Yoo, T.Y. Kang, Validity of SW982 synovial cell line for studying the drugs against rheumatoid arthritis in fluvastatin-induced apoptosis signaling model, Indian J. Med. Res. 139 (1) (2014) 117–124.
[116] A. Rodriguez-Trillo, N. Mosquera, C. Pena, F. Rivas-Tobío, A. Mera-Varela, A. Gonzalez, C. Conde, Non-canonical WNT5A signaling through RYK contributes to aggressive phenotype of the rheumatoid fibroblast-like synoviocytes, Front. Immunol. 11 (2020), 555245.
[117] J. Wen, J. Liu, X. Wang, J. Wang, Expression and clinical significance of circular RNAs related to immunity and inflammation in patients with rheumatoid arthritis, Int. Immunopharmacol. 92 (2021), 107366.
[118] Q. Ouyang, J. Wu, Z. Jiang, J. Zhao, R. Wang, A. Lou, D. Zhu, G.P. Shi, M. Yang, Microarray expression profile of circular RNAs in peripheral blood mononuclear cells from rheumatoid arthritis patients, Cell. Physiol. Biochem. 42 (2) (2017) 651–659.
[119] Q. Luo, L. Zhang, X. Li, B. Fu, Z. Deng, C. Qing, R. Su, J. Xu, Y. Guo, Z. Huang, J. Li, Identification of circular RNAs hsa_circ_0044235 in peripheral blood as novel biomarkers for rheumatoid arthritis, Clin. Exp. Immunol. 194 (1) (2018) 118–124.
[120] X. Tang, J. Wang, X. Xia, J. Tian, K. Rui, H. Xu, S. Wang, Elevated expression of ciRS-7 in peripheral blood mononuclear cells from rheumatoid arthritis patients, Diagn. Pathol. 14 (1) (2019) 11.
[121] Q. Luo, J. Liu, B. Fu, L. Zhang, Y. Guo, Z. Huang, J. Li, Circular RNAs Hsa_circ_0002715 and Hsa_circ_0035197 in peripheral blood are novel potential biomarkers for new-onset rheumatoid arthritis, Dis. Markers 2019 (2019), 2073139.
[122] Q. Ouyang, C. Liu, X. Lu, R. Liang, J. Zhao, M. Yang, Identification of circular RNAs Circ_0005008 and Circ_0005198 in plasma as novel biomarkers for new-onset rheumatoid arthritis, Front. Pharmacol. 12 (2021), 722017.
[123] J. Li, R. Hou, X. Niu, R. Liu, Q. Wang, C. Wang, X. Li, Z. Hao, G. Yin, K. Zhang, Comparison of microarray and RNA-Seq analysis of mRNA expression in dermal mesenchymal stem cells, Biotechnol. Lett. 38 (1) (2016) 33–41.
[124] X. Yang, J. Li, Y. Wu, B. Ni, B. Zhang, Aberrant dysregulated circular RNAs in the peripheral blood mononuclear cells of patients with rheumatoid arthritis revealed by RNA sequencing: novel diagnostic markers for RA, Scand. J. Clin. Lab. Invest. 79 (8) (2019) 551–559.
[125] S. Zhong, Q. Ouyang, D. Zhu, Q. Huang, J. Zhao, M. Fan, Y. Cai, M. Yang, Hsa_circ_0088036 promotes the proliferation and migration of fibroblast-like synoviocytes by sponging miR-140-3p and upregulating SIRT 1 expression in rheumatoid arthritis, Mol. Immunol. 125 (2020) 131–139.
[126] Q. Luo, L. Zeng, J. Rao, L. Zhang, Y. Guo, Z. Huang, J. Li, Expression and clinical significance of circular RNAs hsa_circ_0000175 and hsa_circ_0008410 in peripheral blood mononuclear cells from patients with rheumatoid arthritis, Int. J. Mol. Med. 45 (4) (2020) 1203–1212.
[127] Y. Gao, F. Yao, J. Rao, L. Zhang, Y. Guo, Z. Huang, Q. Huang, J. Li, Q. Luo, Circular RNAs hsa-circ0000175 and hsa-circ0044235 in plasma are novel biomarkers for new-onset rheumatoid arthritis, Autoimmunity 54 (4) (2021) 234–242.
[128] Y. Chen, X. Xu, X. Li, J. Zhong, B. Wu, J. Shang, N. Jiang, B. Wang, S. Zhong, H. Lu, Identification of circular RNAs hsa_circ_0140271 in peripheral blood mononuclear cells as a novel diagnostic biomarker for female rheumatoid arthritis, J. Orthop. Surg. Res. 16 (1) (2021) 647.
[129] X. Wang, R. Ma, W. Shi, Z. Wu, Y. Shi, Emerging roles of circular RNAs in systemic lupus erythematosus, Mol. Ther.–Nucleic Acids 24 (2021) 212–222.
[130] G.C. Tsokos, Autoimmunity and organ damage in systemic lupus erythematosus, Nat. Immunol. 21 (6) (2020) 605–614.
[131] H. Liu, Y. Zou, C. Chen, Y. Tang, J. Guo, Current understanding of circular RNAs in systemic lupus erythematosus, Front. Immunol. 12 (2021), 628872.
[132] F. Zheng, X. Yu, D. Tang, X. Hong, X. Zhang, D. Liu, Y. Dai, The identification of circular RNAs from peripheral blood mononuclear cells in systemic lupus erythematosus, BMC Med. Genet. 14 (1) (2021) 70.
[133] H. Li, K. Li, W. Lai, X. Li, H. Wang, J. Yang, S. Chu, C. Kang, Y. Qiu, Comprehensive circular RNA profiles in plasma reveals that circular RNAs can be used as novel biomarkers for systemic lupus erythematosus, Clin. Chim. Acta 480 (2018) 17–25.
[134] M.Y. Zhang, J.B. Wang, Z.W. Zhu, L.J. Li, R.S. Liu, X.K. Yang, R.X. Leng, X.M. Li, H.F. Pan, D.Q. Ye, Differentially expressed circular RNAs in systemic lupus erythematosus and their clinical significance, Biomed. Pharmacother. 107 (2018) 1720–1727.
[135] S. Li, J. Zhang, X. Tan, J. Deng, Y. Li, Y. Piao, C. Li, W. Yang, W. Mo, J. Sun, F. Sun, T. Han, J. Wang, W. Kuang, Microarray expression profile of circular RNAs and mRNAs in children with systemic lupus erythematosus, Clin. Rheumatol. 38 (5) (2019) 1339–1350.
[136] C. Zhang, J. Huang, Y. Chen, W. Shi, Low expression and clinical value of hsa_circ_0049224 and has_circ_0049220 in systemic lupus erythematous patients, Med. Sci. Monit. 24 (2018) 1930–1935.
[137] X. Wang, C. Zhang, Z. Wu, Y. Chen, W. Shi, CircIBTK inhibits DNA demethylation and activation of AKT signaling pathway via miR-29b in peripheral blood mononuclear cells in systemic lupus erythematosus, Arthritis Res. Ther. 20 (1) (2018) 118.
[138] H. Tang, G. Tan, Q. Guo, R. Pang, F. Zeng, Abnormal activation of the Akt-GSK3beta signaling pathway in peripheral blood T cells from patients with systemic lupus erythematosus, Cell Cycle 8 (17) (2009) 2789–2793.
[139] H. Wu, M. Zhao, L. Tan, Q. Lu, The key culprit in the pathogenesis of systemic lupus erythematosus: aberrant DNA methylation, Autoimmun. Rev. 15 (7) (2016) 684–689.
[140] Q. Miao, Z. Zhong, Z. Jiang, Y. Lin, B. Ni, W. Yang, J. Tang, RNA-seq of circular RNAs identified circPTPN22 as a potential new activity indicator in systemic lupus erythematosus, Lupus 28 (4) (2019) 520–528.
[141] Q. Luo, L. Zhang, X. Li, B. Fu, Y. Guo, Z. Huang, J. Li, Identification of circular RNAs hsa_circ_0044235 and hsa_circ_0068367 as novel biomarkers for systemic lupus erythematosus, Int. J. Mol. Med. 44 (4) (2019) 1462–1472.
[142] G. Guo, H. Wang, L. Ye, X. Shi, K. Yan, K. Lin, Q. Huang, B. Li, Q. Lin, L. Zhu, X. Xue, H. Zhang, Hsa_circ_0000479 as a novel diagnostic biomarker of systemic lupus erythematosus, Front. Immunol. 10 (2019) 2281.
[143] Q. Luo, L. Zhang, L. Fang, B. Fu, Y. Guo, Z. Huang, J. Li, Circular RNAs hsa_circ_0000479 in peripheral blood mononuclear cells as novel biomarkers for systemic lupus erythematosus, Autoimmunity 53 (3) (2020) 167–176.
[144] Q. Luo, X. Li, B. Fu, L. Zhang, L. Fang, C. Qing, Y. Guo, Z. Huang, J. Li, Expression profile and diagnostic value of circRNAs in peripheral blood from patients with systemic lupus erythematosus, Mol. Med. Rep. 23 (1) (2021).
[145] C.-X. Liu, X. Li, F. Nan, S. Jiang, X. Gao, S.-K. Guo, W. Xue, Y. Cui, K. Dong, H. Ding, Structure and degradation of circular RNAs regulate PKR activation in innate immunity, Cell 177 (4) (2019) 865–880, e21.
[146] J.C. Crispín, V.C. Kyttaris, C. Terhorst, G.C. Tsokos, T cells as therapeutic targets in SLE, Nat. Rev. Rheumatol. 6 (6) (2010) 317–325.
[147] L.J. Li, Z.W. Zhu, W. Zhao, S.S. Tao, B.Z. Li, S.Z. Xu, J.B. Wang, M.Y. Zhang, J. Wu, R.X. Leng, Y.G. Fan, H.F. Pan, D.Q. Ye, Circular RNA expression profile and potential function of hsa_circ_0045272 in systemic lupus erythematosus, Immunology 155 (1) (2018) 137–149.
[148] C. Zhang, X. Wang, Y. Chen, Z. Wu, W. Shi, The down-regulation of hsa_circ_0012919, the sponge for miR-125a-3p, contributes to DNA methylation of CD11a and CD70 in CD4(+) T cells of systemic lupus erythematous, Clin. Sci. (Lond.) 132 (21) (2018) 2285–2298.
[149] M. Zhao, Y. Sun, F. Gao, X. Wu, J. Tang, H. Yin, Y. Luo, B. Richardson, Q. Lu, Epigenetics and SLE: RFX1 downregulation causes CD11a and CD70 overexpression by altering epigenetic modifications in lupus CD4+ T cells, J. Autoimmun. 35 (1) (2010) 58–69.
[150] J. Luan, C. Jiao, W. Kong, J. Fu, W. Qu, Y. Chen, X. Zhu, Y. Zeng, G. Guo, H. Qi, L. Yao, J. Pi, L. Wang, H. Zhou, circHLA-C plays an important role in lupus nephritis by sponging miR-150, Mol. Ther.–Nucleic Acids 10 (2018) 245–253.
[151] S.C. Ng, H.Y. Shi, N. Hamidi, F.E. Underwood, W. Tang, E.I. Benchimol, R. Panaccione, S. Ghosh, J.C.Y. Wu, F.K.L. Chan, J.J.Y. Sung, G.G. Kaplan, Worldwide incidence and prevalence of inflammatory bowel disease in the 21st century: a systematic review of population-based studies, Lancet 390 (10114) (2017) 2769–2778.
[152] N.A. Molodecky, I.S. Soon, D.M. Rabi, W.A. Ghali, M. Ferris, G. Chernoff, E. I. Benchimol, R. Panaccione, S. Ghosh, H.W. Barkema, G.G. Kaplan, Increasing

incidence and prevalence of the inflammatory bowel diseases with time, based on systematic review, Gastroenterology 142 (1) (2012) 46–54, e42; quiz e30.
[153] Y. Hayashi, H. Nakase, The molecular mechanisms of intestinal inflammation and fibrosis in Crohn's Disease, Front. Physiol. 220 (2022).
[154] Y. Ye, Z. Pang, W. Chen, S. Ju, C. Zhou, The epidemiology and risk factors of inflammatory bowel disease, Int. J. Clin. Exp. Med. 8 (12) (2015) 22529.
[155] P. Chen, G. Zhou, J. Lin, L. Li, Z. Zeng, M. Chen, S. Zhang, Serum biomarkers for inflammatory bowel disease, Front. Med. (Lausanne) 7 (2020) 123.
[156] J. Lin, Q. Cao, J. Zhang, Y. Li, B. Shen, Z. Zhao, A.M. Chinnaiyan, M.P. Bronner, MicroRNA expression patterns in indeterminate inflammatory bowel disease, Mod. Pathol. 26 (1) (2013) 148–154.
[157] Y.A. Hu, Y. Zhu, G. Liu, X. Yao, X. Yan, Y. Yang, W. Wang, X. Zou, X. Li, Expression profiles of circular RNAs in colon biopsies from Crohn's disease patients by microarray analysis, J. Clin. Lab. Anal. 35 (6) (2021), e23788.
[158] L. Lin, G. Zhou, P. Chen, Y. Wang, J. Han, M. Chen, Y. He, S. Zhang, Which long noncoding RNAs and circular RNAs contribute to inflammatory bowel disease? Cell Death Dis. 11 (6) (2020) 456.
[159] Y.L. Ye, J. Yin, T. Hu, L.P. Zhang, L.Y. Wu, Z. Pang, Increased circulating circular RNA_103516 is a novel biomarker for inflammatory bowel disease in adult patients, World J. Gastroenterol. 25 (41) (2019) 6273–6288.
[160] Y.Q. Qiao, C.W. Cai, J. Shen, Q. Zheng, Z.H. Ran, Circular RNA expression alterations in colon tissues of Crohn's disease patients, Mol. Med. Rep. 19 (5) (2019) 4500–4506.
[161] T. Nata, M. Fujiya, N. Ueno, K. Moriichi, H. Konishi, H. Tanabe, T. Ohtake, K. Ikuta, Y. Kohgo, MicroRNA-146b improves intestinal injury in mouse colitis by activating nuclear factor-κB and improving epithelial barrier function, J. Gene Med. 15 (6–7) (2013) 249–260.
[162] X.M. Xu, H.J. Zhang, miRNAs as new molecular insights into inflammatory bowel disease: crucial regulators in autoimmunity and inflammation, World J. Gastroenterol. 22 (7) (2016) 2206–2218.
[163] J. Mudter, M.F. Neurath, Apoptosis of T cells and the control of inflammatory bowel disease: therapeutic implications, Gut 56 (2) (2007) 293–303.
[164] T. Nunes, C. Bernardazzi, H.S. de Souza, Cell death and inflammatory bowel diseases: apoptosis, necrosis, and autophagy in the intestinal epithelium, Biomed. Res. Int. 2014 (2014), 218493.
[165] U.P. Singh, N.P. Singh, E.A. Murphy, R.L. Price, R. Fayad, M. Nagarkatti, P. S. Nagarkatti, Chemokine and cytokine levels in inflammatory bowel disease patients, Cytokine 77 (2016) 44–49.
[166] J. Yin, T. Hu, L. Xu, P. Li, M. Li, Y. Ye, Z. Pang, Circular RNA expression profile in peripheral blood mononuclear cells from Crohn disease patients, Medicine (Baltimore) 98 (26) (2019), e16072.
[167] C. Li, J.F. Kuemmerle, Mechanisms that mediate the development of fibrosis in patients with Crohn's disease, Inflamm. Bowel Dis. 20 (7) (2014) 1250–1258.
[168] J. Zhao, Q. Lu, Y. Liu, Z. Shi, L. Hu, Z. Zeng, Y. Tu, Z. Xiao, Q. Xu, Th17 cells in inflammatory bowel disease: cytokines, plasticity, and therapies, J Immunol Res 2021 (2021), 8816041.
[169] S. Xia, D. Zhang, S. Zheng, C. Wu, Q. Lin, S. Ying, X. Shao, Y. Jiang, Association of Crohn's disease with Foxp3 gene polymorphisms and its colonic expression in Chinese patients, J. Clin. Lab. Anal. 33 (4) (2019), e22835.
[170] N. Dalbeth, T.R. Merriman, L.K. Stamp, Gout, Lancet 388 (10055) (2016) 2039–2052.
[171] M. Dehlin, L. Jacobsson, E. Roddy, Global epidemiology of gout: prevalence, incidence, treatment patterns and risk factors, Nat. Rev. Rheumatol. 16 (7) (2020) 380–390.
[172] K.T. Clebak, A. Morrison, J.R. Croad, Gout: Rapid Evidence Review, Am. Fam. Physician 102 (9) (2020) 533–538.
[173] W.Z. Zhang, Why does hyperuricemia not necessarily induce gout? Biomolecules 11 (2) (2021).
[174] F. Dai, Q.B. Zhang, Y.P. Tang, Y.X. He, T. Yi, Y.F. Qing, Expression profile and potential function of circular RNAs in peripheral blood mononuclear cells in male patients with primary gout, Front. Genet. 12 (2021), 728091.
[175] A.K. So, F. Martinon, Inflammation in gout: mechanisms and therapeutic targets, Nat. Rev. Rheumatol. 13 (11) (2017) 639–647.
[176] Y. Zhang, X. Tan, Z. Lin, F. Li, C. Yang, H. Zheng, L. Li, H. Liu, J. Shang, Fucoidan from laminaria japonica inhibits expression of GLUT9 and URAT1 via PI3K/Akt, JNK and NF-κB pathways in uric acid-exposed HK-2 cells, Mar. Drugs 19 (5) (2021).