Role of circular RNAs in immune-related diseases

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Abstract: Objective Circular RNAs (circRNAs) are non-coding RNAs (ncRNAs) circularized without a 3′ polyadenylation [poly(A)] tail or a 5′ cap, resulting in a covalently closed loop structure. circRNAs were first discovered in RNA viruses in the 1970s, but only a small number of circRNAs were discovered at that time due to limitations in traditional polyadenylated transcriptome analyses. With the development of specific biochemical and computational methods, recent studies have shown the presence of abundant circRNAs in eukaryotic transcriptomes. circRNAs play vital roles in many physiological and pathological processes, such as acting as miRNA sponges, binding to RNA-binding proteins (RBPs), acting as transcriptional regulatory factors, and even serving as translation templates. Current evidence has shown that circRNAs can be potentially used as excellent biomarkers for diagnosis, therapeutic effect evaluation, and prognostic assessment of a variety of diseases, and they may also provide effective therapeutic targets due to their stability and tissue and development-stage specificity. This review focuses on the properties of circRNAs and their immune relationship to disease, and explores the role of circRNAs in immune-related diseases and the directions of future research.

Keywords: circRNA; autoimmune diseases; immunology; genetics; biomarkers

1 Overview of circRNAs

1.1 Discovery and formation of circRNAs

The concept of circRNAs was first reported in 1976 after the discovery of circRNAs in RNA viruses [1]. Thereafter, researchers identified the formation of circRNAs in human cells [2,3], but they were first considered as the products of RNA splicing errors without specific biological functions due to their structure, a ring covalently bound by a 5′ cap and 3′ poly (A) tails without the 5′ cap or the 3′ poly (A) tails. This intrinsic characteristic has enabled them to escape from detection by traditional polyadenylated transcriptome analyses, so that only a few discoveries of circRNAs were made in the past.

With the rapid development of specific biochemical and computational methods, many circRNAs were found in various cell lines of different species including but not limited to fungi, plants, insects, and mammals [4,5]. Studies have shown that circRNAs are highly represented and occur naturally in eukaryotic transcriptomes [2,8]. Most circRNAs are derived from known genes and can be divided into 3 groups according to their constituent sequences: exonic circRNAs (EcRNAs), circular intronic RNAs (ciRNAs), and circRNAs composed of exons and introns (EciRNAs). Most of them are formed by reverse complementation of introns and exon skipping. Recent studies have shown that back-splicing, the way circRNAs are generated and a type of alternative splicing, requires spliceosomal machinery and can be modulated by both cis-regulatory elements and trans-acting factors [5,9,10]. Although most of circRNAs have low expressions, some circRNAs were shown to have higher abundance than their linear counterparts in biological samples [11], suggesting that circRNAs have irreplaceable biological functions under physiological conditions and some circRNAs may even play vital roles in various physiological and pathological processes.

1.2 Biological functions of circRNAs

circRNAs are involved in different physiological
and pathological processes and have a wide range of functions, including miRNA sponging, alternative splicing, RNAP II elongation, RNA maturation regulation, RBP sponging, protein localization, histone modification, and protein translation.

The most widely known circRNA function is their role as competitive endogenous RNAs (ceRNAs), known also as miRNA sponges \([11,12]\). miRNA can bind to the matched 3’ UTR of mRNAs to mediate post-transcriptional silencing of protein-coding genes. Via competing for miRNA binding sites, circRNAs can indirectly regulate the expression of the target mRNAs of miRNA. For instance, cirRS-7 contains more than 60 putative miR-7 target sites and inhibits the binding of miR-7 to mRNA by sponging miR-7 to regulate the expression of miR-7 target mRNAs \([10]\). Testis-specific circRNA sex determining region Y (Sry) contains 16 miR-138 binding sites \([21]\). circHIPK3 can sponge miR-124 and miR-193 to regulate cell growth in cancer \([14]\).

Transcriptional regulation is another widely known function and usually contributes to the alternative splicing of the linear cognates of circRNAs. ElicRNAs and cirRNAs that are confined in the nucleus usually contribute to this type of regulation. For example, circSEP3 can bind to its cognate DNA locus via competing with a linear RNA, leading to the formation of alternatively spliced SEP3 mRNA with exon skipping. Notably, some circRNAs, especially those derived from exon 2, can sequester the translation start site, resulting in the production of non-coding linear transcripts. Additionally, circRNAs are associated with the elongation RNA Pol II machinery. circEIF3J and circPAOP2 increase transcription activity by interacting with U1 nuclear ribonucleoprotein (U1 snRNP). ci-ankrd52 can accumulate at sites of transcription and positively modulate the efficiency of Pol II transcription to indirectly regulate the transcription of its parent gene \([15]\).

circRNAs also participate in protein translation control. circRNAs can impair the activity of rRNA-processing machinery to regulate RNA maturation so that protein translation will be slowed. circANRIL can decrease the interactions of the PocBoW complex member PES1 with pre-rRNA intermediates, which function in pre-mRNA processing during 60S ribosome maturation \([16]\). As RBP sponges, circPABPN1 and circFoxx3 can inhibit proteins that are known to promote the translation of mRNAs, circPABPN1 can bind HuR, which is a well-studied RBP, and interact with multiple linear mRNAs, such as PABPN1 mRNA \([17]\). As a result, the parent linear mRNA of circPABPN1 is affected, and less PABPN1 mRNA can be translated into protein.

circFoxx3 is able to bind with CDK2 and p21 to inhibit the function of CDK2 \([18]\). Apart from binding RBPs, circFoxx3 also regulates protein subcellular localization. circFoxx3 can interact with ID1 and E2F1 in the nucleus. The ectopic expression of circFoxx3, which is predominantly found in the cytoplasm, can facilitate the translocation of most ID1 and E2F1 in a pattern consistent with the distribution of circFoxx3 \([19]\).

At the posttranslational level, circRNAs can participate in histone modification. cANRIL is a circular isoform produced from the non-coding transcripts of the INK4A-ARF-INK4B gene cluster \([20]\). The p15INK4B locus can be bound by polycomb repression complex 2 (PRC2), and histone H3 lysine27 (H3K27) trimethylation can repress the transcription of p15INK4B. cANRIL can bind and recruit PRC2 and is required for the occupancy of the p15INK4B locus by PRC2 \([21]\). Previous studies have indicated that non-coding ANRIL can bind CBX7, a H3K27me3-recognizing component of PRC1, and repress the INK4A and NK4B loci \([22]\). This suggests that circRNAs may play a role in epigenetic regulation.

There is also a special process by which some circRNAs can be translated into functional polypeptides. Two typical circRNAs that go through this process are circZNF609 \([23]\) and circMbl \([24]\). There are at least two requirements for the circRNAs to be translated: one is that back-splicing should occur at the first exon, and the other is that the 5’ UTR of the host gene should have properties similar to the internal ribosome entry sequence (IRES). These IRES-like sequences function independently of their orientation relative to the start codon \([21]\). Although these polypeptides encoded by circRNAs have not yet been found to have fateful physiological functions, the stress conditions in which the splicing-dependent and cap-independent mechanism occurs can broaden our understanding of protein translation in extreme circumstances.

2 CircRNAs in autoimmune diseases

2.1 Rheumatoid arthritis

Rheumatoid arthritis (RA) is a chronic autoimmune syndrome that progressively impairs periphery joints and leads to serious cartilage and bone erosion as well as articular deformation \([25]\). Rheumatoid factor (RF), anti-carbamylated protein (anti-CarbP), and anti-cyclic citrullinated peptide-2 (anti-CCP2) are the most well-known autoantibodies in this disease \([26]\).

PBMCs are closely related to the development of RA. Ouyang et al \([27]\) discovered 9 elevated and 3 repressed circRNAs in RA-associated PBMCs compared with healthy controls and found that hsa_circ_104871, hsa_circ_003524, hsa_circ_101873 and hsa_circ_103047 in PBMCs had diagnostic value in RA. However, the alterations in the levels of these PBMC-related circRNAs are not parallel to the changes observed in the erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) levels, health assessment questionnaire (HAQ) scores and disease activity score (DAS28), suggesting that these circRNAs cannot represent the severity or pathological processes of RA. Similarly, Zheng et al \([28]\) found 584 differentially expressed circRNAs in RA, including 255 overexpressed and 329 knocked-down circRNAs. In particular, these researchers also proposed that the identified circRNAs may act as potential suppressors or inducers during the occurrence of RA. The markedly enhanced expression of the RA promoter miR-181d is
partially due to the repression of hsa_circ_0057980, which is a miR-181d sponge. The altered expression of hsa_circ_0088088 is related to a high level of miR-16, which is an activator of ESR and CRP [36]. In contrast, hsa_circ_0001045 was increased in samples of RA synovialis, which is directly associated with and seriously inhibited miR-30a, thereby reducing cell apoptosis and contributing to RA progression [36]. Intriguingly, the corresponding parental genes of the significantly changed circRNAs in the RA patients, such as polynucleotide kinase 3'-phosphatase (PNKP), ARIgAP with GTPase domain, hydroxysteroid dehydrogenase like 2 (HSD12), ankyrin repeat and PH domain 1 (AGAP1) and protein kinase C beta (PRKCB), also participate in the regulation of RA [30]. It was found that circRNA_09505 might serve as a miR-6089 sponge and mediate inflammation via miR-6089/AKT/NF-κB pathway in CIA mice [32], indicating the role of circRNAs in RA pathogenesis.

2.2 Systemic lupus erythematosus

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease that predominately affects women of childbearing age. Its main features are the autoreactive B and T lymphocytes as well as the overproduction of antibodies targeting antigens [32]. Unfortunately, SLE can result in multi-organ pathologies and a wide range of clinical manifestations, including arthritis, central nervous system disease, renal disease and skin disease [33]. Although SLE is immune-mediated, the pathogenic mechanisms are still not fully understood.

There are over 200 differentially expressed circRNAs in the plasma of SLE patients, of which approximately 127 differentially expressed circRNAs in the PBMCs. Hsa_circ_0077179 (also circIBTK) is downregulated and inversely correlated with the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) score and anti-dsDNA titer in patients [30], circIBTK expression also is positively correlated with the complement C3 levels. The expression of circIBTK is notably elevated when patients achieved significant clinical improvement [34]. Since the AKT signaling pathway may account for the lymphocyte alteration in SLE, an additional study demonstrated that circIBTK could induce DNA methylation and regulate the AKT signaling pathway via miR-29b to regulate the proliferation and apoptosis of CD4+ T cells [34-35]. ROC curve analysis suggests that circIBTK might act as a biomarker and therapeutic target in SLE. In addition, hsa_circ_0045272 is downregulated in the T cells of SLE patients. After hsa_circ_0045272 expression knockdown in Jurkat cells, interleukin-2 production and the early apoptosis was upregulated [36]. Apart from sponging miR-6127, hsa_circ_0045272 can regulate the transcription factors PAX8 and DTX4 at the mRNA level [36]. PAX8 protein can inhibit apoptosis, and DTX4 protein can mediate the regulation of TANK-binding kinase, which is implicated in type I interferon production [37-38], but their mRNA functions independent of protein require experimental verification. Importantly, recent research published by Liu et al [39] showed that overexpression of the dsRNA-containing circRNA in PBMCs or T cells derived from SLE can alleviate the aberrant PKR activation cascade, thus suggesting the significant relationship between circRNAs and SLE.

2.3 Multiple sclerosis

Multiple Sclerosis (MS) is a chronic disease of the central nervous system (CNS), and diffuse immune mechanisms as well as neuroregeneration are the underlying pathological processes in this disease. The peripheral immune response targeting the CNS occurs mainly in the early stage of MS, whereas immune process within the CNS dominates the progressive stage [40]. Most patients will develop permanent disability during the course of their disease, creating a huge burden for individual, family and society levels [41].

Over 400 circRNAs are differentially expressed in the PBMCs of relapsing-remitting multiple sclerosis (RRMS) patients compared with those of healthy controls. Hsa_circ_0106803, which is an alternative splicing abnormality of the GSDMB gene, exhibits a 2.8-fold expression upregulation in PBMCs in RR-MS [42]. As predicted by the PITA algorithm, Hsa_circ_0106803 has more than 2 miRNA targets, such as miR-1275 and miR-149, which can contribute to susceptibility to MS. [42-44]. It was reported that miR-1275 can promote cell migration, invasion and proliferation. miR-149 can bind to ASIC1, which is a key subunit determining acid activated currents in neurons, and reduce ASIC1 expression. Therefore, hsa_circ_0106803 might regulate the expression of ASIC1 by sponging miR-149 to modulate the progression of MS. In addition, two circRNAs from ANXA2, hsa_circ_0005402 and hsa_circ_0003452_2, are under-expressed in the PBMCs of patients. ANXA2 was reported to be a target of miR-155, whose expression increases greatly in PBMCs and correlates with disease severity in MS patients [45]. Hsa_circ_0005402 shares 14 common miRNA targets with hsa_circ_0003452_2, suggesting cooperative regulation of the circRNA-miRNA- mRNA axis [46]. Another circRNA profile carried out by Zurawksa et al [47] in patients with RRMS and healthy controls defined that circRNAs in the known disturbed B-cell activity in RRMS may act as a novel biomarker for monitoring relapse activity.

2.4 Primary biliary cholangitis

Primary biliary Cholangitis (PBC), which is also called primary biliary cirrhosis, primarily destroys the small intrahepatic bile ducts, leading to hepatic fibrosis or cirrhosis. In general, patients with PBC are always in a severe disease state at diagnosed due to their typically asymptomatic conditions during the early stages. Hence, the identification of sensitive biomarkers for the early diagnosis of PBC is urgently needed.

Ursodeoxycholic acid (UDCA) is the current first-line therapy for primary biliary cholangitis (PBC). There are 22 circRNAs differentially expressed in the
plasma of PBC patients versus that of healthy individuals. In a study on the influence of UDCA treatment, hsa_circ_402458 was selected as a biomarker because its expression was significantly higher in PBC patients who were not receiving therapy than those receiving therapy \[48\]. The ROC analysis showed that hsa_circ_402458 had the diagnostic value with the highest sensitivity and specificity for PBC among the candidates. In addition, hsa_circ_402458 is predicted to target two miRNAs, miR-522-3p and miR-943, which are involved in the abnormal resolution of inflammation and TGF-β pathway, respectively. Therefore, hsa_circ_402458 may function as a miRNA sponge to regulate inflammation-related pathways, contributing to the pathogenesis and development of PBC.

2.5 CircRNAs in virus infections

Recent studies have reported significant role and diverse biological functions of circRNAs in viral infections as well as in the regulation of innate immune responses. Both host and virus-derived circRNAs have been reported to interact with double-stranded RNA (dsRNA)-binding antiviral proteins and regulate immune responses during host virus interactions \[45,50\]. In the antiviral innate immune system, dsRNA-binding proteins are key factors and play an essential role by inducing a variety of alterations in cellular and viral RNA processes to repress viral replication. The work by Chen et al \[44\] revealed that exogenous circRNAs can trigger an innate immune response which confers protection against viral infection. The authors reported that circRNAs potently induced the expression of several regulatory genes of the innate immune system including retinoic-acid-inducible gene-I (RIG-I), protein kinase R (PKR), melanoma-differentiation-associated gene 5 (MDA5), 2′-5′ oligoadenylate synthase 1 (OAS1), and OAS-like protein (OASL) in different cell lines. The authors further tested whether the innate immune response generated by exogenous circRNAs can significantly influence the ability of a virus to infect cells. Results unveiled that cell transfected with circRNAs had a 10-fold lower infection rate compared to control cells. Moreover, further findings revealed that the activation of immune responses in the context of viral infections depends on the splicing mechanism of circRNAs as circRNAs only made with self-splicing introns were able to activate RIG-I \[40\]. In another study, Li et al \[30\] reported that dsRNA-binding proteins namely NF90 and NF110 (products of ILF3 gene) may enhance the biogenesis of circRNAs by promoting their production in the nucleus. The authors identified genes involved in host-circRNA biogenesis by utilizing genome-wide short hairpin RNA (shRNA) library screening. They reported that in addition to their involvement in circRNA biogenesis, these dsRNA-binding proteins preferred to bind circRNAs compared to linear RNAs. Their study revealed the formation and accumulation of NF90/NF110-circRNP complexes in the cytoplasm. Furthermore, their results suggested that circRNAs compete with viral mRNAs for NF90/NF110 binding. Upon viral infection, circRNA production is decreased as a result of nuclear export of NF90/ NF110 to the cytoplasm. Meanwhile, NF90 and NF110 are released from circRNA-protein complexes (circRNPs) and binds to viral mRNAs as a part of their functions in the antiviral immune response. The authors concluded that upon viral infection, circRNAs can function as a molecular reservoir of NF90/NF110 for rapid immune response whereas in the non-infected circumstances, the association of NF90/ NF110 with circRNAs may keep them from non-specific immune responses in the cell.

2.6 CircRNAs in cancer immunity

The close relationship between circRNAs and miRNAs lays the foundation for circRNAs to participate in the regulation of antitumor immune responses. As previously reported \[51\], hsa_circ_0020397 induces the expression of telomerase reverse transcriptase (TERT) and PD-L1 by binding and inhibiting the activity of miR-138 in colorectal cancer (CRC) cells. In fact, the interaction between PD-1 and PD-L1 on specific tumor cell surfaces exhausts immunocytes and promotes immune escape. Circ-Amot111 can indirectly restrain the presence of miR-17-5p by upregulating Dmnt3a, which may induce a highly DNA methylation enriched condition in the promoter region of miR-17, leading to the elevated expression and subcellular translocation of STAT3, launching tumor-mediated immune inhibition \[52\]. These studies suggest that circRNAs can modulate the expression and functions of immune-related miRNAs at the transcriptional or posttranscriptional level in immune responses against tumors.

Additionally, it has been uncovered that circRNAs are involved in antitumor immunity through binding with dsRNA sensors and transcription factors, circNDUFB2, reported by Li et al \[53\], recruits DCs and CD8+ T cells into tumor microenvironment by activating the RIG-I - MAVS pathway and then boosting the secretion of chemokines in NSCLC. Transcription of PD-L1 in nasopharyngeal carcinoma is promoted by circBART2.2 binding to the helicase domain of RIG-I \[54\], circFAT1 mediates its effects in NHSCC by binding directly to STAT3 in the cytoplasm and preventing STAT3 dephosphorylation by SHP1, leading to cancer stemness and immune evasion. Knockdown of circFat1 significantly increases CD8+ T cell infiltration by inducing Type 1 IFN \[55\]. Further explorations focusing on circRNA-miRNA and circRNA-RBP interactions are likely to provide new insight into tumor immunotherapy.

3 CircRNAs in other immune-related diseases

3.1 Osteoarthritis

Osteoarthritis (OA) is a chronic joint-retrogressive lesion with articular cartilage degradation and inflammation. Studies have reported that circRNAs mediate the pathogenesis of OA in an IL-1β-induced
manner by sponging certain miRNAs [56]. Circ-Atp9b and hsa_circ_0005105 suppress the expression of type II collagen, enhance the functions of matrix metallopeptidase 13 (MMP-13) and promote the generation of IL-6 and IL-8 by targeting miR-138-5p and miR-26a, respectively, to activate the biogenesis of OA [57,58]. Additionally, circRNAs participate in the signaling pathway of TNF-α, which is a vital inflammatory factor in OA, to induce damage to cartilage cells [59]. Intriguingly, circRNAs not only play a pathogenic role but also protect our bodies from OA lesions. Li et al [60] verified that hsa_circ_0045714 elevates proliferation in cartilage cells and increases the expression of type II collagen and aggrecan by sponging miR-193b, which strengthened the functions of insulin like growth factor 1 receptor (IGF1R), a biotarget of miR-193b and a negative regulator of OA. Similarly, circ-VMA21 can alleviate inflammatory cytokine-induced apoptosis in nuclei pulposus cells and catabolism of the extracellular matrix (ECM) through the miR-200c-3p-XIAP pathway during intervertebral disc degeneration (IVDD) [61]. Shen et al revealed the protective effect of CircDK14 mediated by miR-125a-5p/Smad2 axis, which leads to the dysfunction of TGF-β signaling pathway in OA progression [62]. Zhu et al elucidated a novel circRNA, circGCN1L1, induces inflammation synoviocytes and decreases anabolism of the ECM through targeting miR-330-3p, which is associated with condylar chondrocyte apoptosis and synoviocyte hyperplasia in TMJ osteoarthritis [63]. In summary, the evidence above indicated that circRNAs are important regulators of pathogenesis and potential therapeutic targets for OA.

3.2 Fibrosis

Fibrosis is the comprehensive result of chronic inflammation caused by constant stimulation by infection, allergic response and tissue injury [64]. Studies have revealed that circRNAs induce fibrosis progression in diverse organs. The long-term inhalation of large amounts of silica is a key inducer of lung fibrosis. SiO2-induced pulmonary fibrosis is accompanied by a high expression level of circ-ZC3H4. Circ-ZC3H4 can increase the presence of zinc finger CCCH-type containing 4 (ZC3H4) by restricting miR-212 as an endogenous competitor through its binding sites, thereby elevating proliferation and migration in alveolar macrophages and fibroblasts after exposure to SiO2 [65]. The work of Li et al [66] revealed that circTADA2A repressed lung-fibroblasts activation via miR-526h/Cav1 and reduced lung-fibroblasts proliferation via miR-203/Cav2, thus inhibiting the excessive deposition of ECM and relieving idiopathic pulmonary fibrosis. Liver fibrosis is inseparable from the activation of hepatic stellate cells (HSCs). HSCs are the dominant source of the ECM and can transform into myo-fibroblastic-like cells, highlighting their critical pro-fibrosis functions. The prolonged stimulation of pro-inflammatory factors dramatically initiates the activation of HSCs. Studies have clarified that the inhibition of hsa_circ_0071410 increases the expression of miR-9-5p, leading to the attenuation of HSC activation in several immune-associated pathways [67]. Downregulation of circRNA_010383 was identified for promoting proteinuria and renal fibrosis in diabetic nephropathy by acting as a sponge for miR-135a [68]. Hsa_circ_010567 can also promote myocardial fibrosis by inhibiting the expression level of miR-141 through the initiation of TGF-β1 signaling and expanding the effects of circRNAs on fibrosis and the cardiovascular system [69]. circ-Yap, was found to attenuate cardiac fibrosis via binding with Tropomyosin-4 and gamma-actin decreasing actin polymerization in mouse hearts [70]. Moreover, recent study uncovered that circHIPK3 contributes to increasing myocardial fibrosis during diabetic cardiomyopathy through functioning as a ceRNA for miR-29b-3p [71]. Further exploration is required to investigate the roles played by circRNAs in organ fibrosis.

4 Discussion and conclusion

Mechanistic and functional studies have shown that circRNAs are not simply useless by-products. Our current knowledge of circRNAs is still poor, and they are worthy of further research. As their various functions are being discovered, circRNAs show great research potential, similar to miRNAs and IncRNAs. Studying the relationships between circRNAs and diseases has important clinical implications, including but not limited to discoveries related to pathological roles, diagnostic potential, and therapeutic effects.

Based on findings in current studies, the majority of circRNAs found in autoimmune diseases are EcRNAs, and a few are ciRNAs and EIciRNAs [72]. As circRNAs have close relationships with autoimmune diseases, the combined detection of different circRNAs and transitional markers may improve the efficiency of clinical diagnosis. Besides, circRNAs might be artificially synthesized for achieving miRNA loss-of-function in vitro. Recently, synthetic circRNA was verified to sponge miR-21 and increase the expression of miR-21 downstream proteins, while successfully suppressing gastric carcinoma cell proliferation [73]. This provides a potential strategy for seeking therapeutic targets in the future. circRNA-based therapy should be delivered to the specific target cells which are still unknown. Considering that circRNAs function as miRNA sponges and RBPs sponges, circRNAs often have several targets, which makes ceRNA networks more complicated and enhances the difficulty in improving curative effect of circRNA-based therapy. Although many circRNAs are under investigation, their roles in autoimmune diseases remain elusive. Advances in the methods, construction of circRNA databases and further study of circRNAs will be crucial to determine their mechanisms in autoimmune diseases.

The significance of circRNA-mediated antiviral immune responses has been unveiled in recent years. By regulating the expression of gene related to innate
immunity, circRNAs have been reported to provide protection against viral infections. Moreover, as a key regulator in circRNA biogenesis, cellular immune factors can also play a critical role in inhibiting viral infections. Despite the recent advances, the current understandings in the study of the significance of circRNAs in viral infections and antiviral immune responses are limited, as there are still an enormous number of circRNAs with unknown functions within the eukaryotic transcriptome. Further studies are warranted to fully elucidate the multifaceted interplays between circRNAs and the host immune system in antiviral defence responses, which will not only increase our understanding of the physiological function of circRNAs but also provide potential therapeutic strategies against viral diseases. In the light of above-mentioned studies, both host-derived endogenous circRNAs (which provide defense against viral infections) as well virus-encoded exogenous circRNAs could be exploited therapeutically to prevent viral infections.

Although our current knowledge of circRNAs is preliminary, it is reasonable to speculate about the promising perspective of deeper explorations of these ncRNAs regarding gene regulation and immune disease occurrence. The observed differential expression levels of circRNAs between normal tissues and diseased tissue indicate that circRNAs probably play important physiological and pathological roles. CircRNAs are highly conserved, quite stable and very appropriate as biomarkers for some immune diseases. Moreover, circRNAs can be exploited as therapeutic targets because the overexpression of specific circRNAs can suppress the pro-immune disease miRNA level via their miRNA sponge. Optimizing antisense approaches to alter the splicing pattern in order to produce more beneficial circRNAs that block or postpone the development and progression of immune diseases might be a feasible strategy. It is expected that the development of new technologies will contribute to the discovery of more diagnosis- and prognosis-related circRNAs and that therapeutics depending on circRNAs will be formulated, thereby providing new perspectives and directions for the identification and treatment of immune diseases.

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环状RNA在免疫相关疾病中的作用

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摘要：环状RNA（circRNAs）是一种无3’聚腺苷酸(poly-[A])尾或5’帽的共价闭环结构非编码RNA（ncRNA），是一个崭新的研究领域。环状RNA最早于20世纪70年代在RNA病毒中被发现，但由于传统的多重聚腺苷酸转录组分析的局限性，最初发现的circRNAs数量很少。由于特定的生化和计算方法的发展，近年来的研究表明，大量circRNAs在真核转录组中自然而广泛地存在。研究发现circRNAs在多种生理和病理过程中发挥重要作用，如充当miRNA海绵、与RNA结合蛋白（RBP）结合、作为转录调控因子，甚至作为翻译模板。研究者认为circRNAs可能是与各种疾病的诊断、疗效和预后相关的潜在生物标志物，由于其稳定性和组织及发育阶段的特异性，可能成为有效的治疗靶点。本综述重点讨论circRNAs的特性和其免疫功能并揭示其在免疫相关疾病中的作用。

关键词：环状RNA；自身免疫疾病；免疫学；基因学；生物标志物

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