REVIEW ARTICLE

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Circular RNAs in the pathogenesis of sepsis and their clinical implications: A narrative review

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ABSTRACT

Introduction: Sepsis is defined as a life-threatening complication that occurs when the body responds to an infection attacking the host. Sepsis rapidly progresses and patients deteriorate and develop septic shock, with multiple organ failure, if not promptly treated. Currently no effective therapy is available for sepsis; therefore, early diagnosis is crucial to decrease the high mortality rate. Genome-wide expression analyses of patients in critical conditions have confirmed that the expression levels of the majority of genes are changed, suggesting that the molecular basis of sepsis is at the gene level. This review aims to elucidate the role of circular (circ) RNAs in the pathogenesis of sepsis and sepsis-induced organ damage. In addition, the feasibility of using circRNAs as novel diagnostic biomarkers for sepsis is also discussed, as well as circRNA-based therapy.

Method: This narrative review is based on a literature search using Medline database. Search terms used were "circular RNAs and sepsis", "circRNAs and sepsis", "non-coding RNAs and sepsis", "ncRNAs and sepsis", "circRNAs and septic pathogenesis", "circRNAs and septic model", "circRNAs and septic shock" and "circRNAs, biomarker, and sepsis".

Results: Numerous studies indicate that circRNAs might exert pivotal roles in regulating the immune system of the host against various pathogens, such as bacteria and viruses. Dysregulation of circRNA expression levels has been confirmed as an early event in sepsis and associated with the inflammatory response, immunosuppression and coagulation dysfunction. This impairment in regulation eventually leads to multiple organ dysfunctions, including of the kidneys, lungs and heart.

Conclusion: By investigating the regulation of circRNAs in sepsis, new molecular targets for the diagnosis and intervention of sepsis can be identified. Such an understanding will be important for the development of therapeutic drugs.

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Keywords: Acute kidney injury, biomarker, circRNAs, inflammation, sepsis

INTRODUCTION

Sepsis is a condition with life-threatening organ dysfunction, resulting from abnormal responses of the host to various infections.[1] The underlying pathogenic mechanisms include an imbalanced inflammatory response, immune disorder, neuroendocrine abnormality, coagulopathy, mitochondrial damage and endoplasmic reticulum stress.[2] A recent study reported that the age-standardised sepsis incidence rate fell by 37.0% and the mortality rate decreased by 52.8% from 1990 to 2017.[3] Despite the declining incidence and mortality rates, sepsis is still a global problem, with the highest health-related burden in sub-SaharanAfrica.[3]

Biomarkers can be used in clinics to evaluate the pathophysiological process of various diseases, and play important roles in assisting the diagnosis, monitoring the efficacy of treatment and influencing the prognosis. There have been >170 biomarkers identified that are associated with sepsis; however, the majority of them lack sensitivity or specificity, and only a few have been used in the clinical diagnosis of infections, including C-reactive protein, procalcitonin, high mobility group protein B-1,

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CLINICAL IMPACT

What is New

- This review provides an update on the understanding of circular RNAs (circRNAs) in the pathogenesis of sepsis and the associated organ dysfunction. It investigates their feasibility as effective and efficient diagnostic and therapeutic biomarkers for sepsis.

Clinical Implications

- The understanding of circRNA-modulated sepsis-induced organ failure is still at a very early stage. Thus, further research is urgently required to investigate the regulation of circRNAs in the progression of different diseases, and to identify specific circRNAs in certain diseases.

interleukins and soluble triggering receptor expressed on myeloid cells-1.[4] Therefore, the severity and recovery of sepsis cannot be objectively evaluated, which limits the wide application of these biomarkers in a clinical setting. Thus, identification of more effective biomarkers is an urgent need to improve diagnosis/prognosis.

Circular (circ) RNAs are newly identified endogenous non-coding RNAs formed by exon scrambling during the splicing process. They are typically covalently closed-loop molecules, which distinguish them from the other 2 linear non-coding RNAs—microRNAs (miRNA/miR) and long non-coding RNAs—which possess caps at the 5' terminal and tails at 3' terminal.[5] With rapid evolution of high-throughput sequencing techniques, circRNAs have been found to be widely distributed in various eukaryotes. They exert significant roles in gene transcription and participate in a range of cellular events such as cell differentiation, apoptosis, autophagy and proliferation, which are all associated with septic pathogenesis.[6] Here, we provide an update on the progress of our understanding of circRNAs in the pathogenesis of sepsis and the associated organ dysfunction. We also investigate their feasibility as effective and efficient diagnostic and therapeutic biomarkers for sepsis.

METHOD

This narrative review is based on a literature search of the Medline database. Search terms used were "circular RNAs and sepsis", "circRNAs and sepsis", "non-coding RNAs and sepsis", "ncRNAs and sepsis", "circRNAs and septic pathogenesis", "circRNAs and septic model", "circRNAs and septic shock" and "circRNAs, biomarker, and sepsis".

Overview of circRNAs

circRNAs have a stable structure, are highly expressed, have specific tissue distribution patterns and are highly conserved among different species.[7] They are widespread and substantial within transcriptomes, an observation confirmed using high-throughput sequencing and analysis platforms.[8] circRNAs are principally derived from exons of protein-coding genes and generally formed via the cyclisation of special mRNAs by reverse splicing, which produces covalently closed-loop structures with a length of about 100 nucleotides.[9] circRNAs are generated by multiple mechanisms, including cyclisation via lariat, intron pairing or RNA binding protein pairing. circRNAs cannot be cut by RNA exonuclease.[10] In addition, based on their origin of biogenesis, circRNAs are categorised into exon-, intron-, exon-intron-, and intergenic circRNAs.[11]

Many circRNAs have been indicated to function as "miRNA sponges" to regulate miRNAs in various body fluids and to also function as protein sponges to determine the concentration of proteins in cells.[5] circRNAs have a longer half-life than their homologues and show good stability.[12] It is well-known that circRNAs are not simply the by-products from mis-splicing; instead they are actively involved in pathological processes of diverse diseases.[13] miRNAs have been found to be differentially expressed during the development of sepsis, suggesting certain circRNAs might also be involved. For example, circ_0091702 was found to serve as a sponge for miR-545-3p to alleviate sepsis-induced acute kidney injury (AKI) by increasing the expression level of thrombospondin 2.[14] These biological characteristics and physiological functions suggest that circRNAs have the potential to be septic biomarkers.

In addition, as miRNA sponges, circRNAs also function as a "miR reservoir". For example, circ-HIAT1 was found to target miR-29a-3p and miR-29c-3p, and increase the stability of miRNAs in human atherosclerosis and cancer.[15] In solid tumours, circ-HIAT1 was found to target matrix metalloproteinases that were increased in both the serum and lung tissues in patients with severe sepsis.[16] The high serum level of miR-29a-3p secreted by immune cells has shown a prognostic value in evaluating the 28-day mortality rate in patients with sepsis, while circ-MYLK and circ-CTDP1 have shown a modulatory role in the expression levels of miR-29a-3p.[17]

circRNAs in sepsis-related inflammation

miRNAs have been confirmed to regulate the cytokine storm of sepsis. For example, miRNAs regulated the differential expression of many key cytokines that were involved in sepsis, including TNF-α, IL-6, IL-10 and IL-18.[18] circRNAs have been proposed to exert essential

roles during different stages of sepsis by regulating lipopolysaccharide (LPS)-induced inflammation and the activation of NF-κB signalling via sponging miRNAs. A recent study found that knockdown of circ_0114428 expression inhibited cereblon expression, and attenuated LPS-induced inflammation and oxidative stress in human kidney 2 (HK2) cells by sponging miR-495-3p.[19] Xiong et al. found that the knockdown of circ_0003420 expression could attenuate the effect of LPS on cell apoptosis, proliferation and inflammation by targeting NPAS4 mRNA.[20] Wei et al. showed that overexpression of hsa_circ_0068,888 could suppress the LPS-induced inflammatory response and oxidative stress, while knockdown of expression could increase these processes.[21] A further study found that hsa_circ_0068,888 inhibited the activation of NF-κB signalling by sponging miR-21-5p.[21] Furthermore, Liu et al. found that circ_0001105 protected the integrity of the intestinal barrier from intestinal inflammation and oxidative stress in septic rats, providing a new perspective to treat sepsis.[22]

circRNAs in sepsis-related immunosuppression

The majority of patients with sepsis may die during the early stage of the cytokine storm. Patients who survive this stage can exhibit immunosuppression—they fail to eliminate primary infections, develop secondary opportunistic infections, and viruses can potentially reactivate—which seriously affects their survival.[2] circMAN2B2, a circRNA abundant in glioma tissues, was found to regulate S100A8 expression levels by inhibiting miR-1205.[23] S100A8 is known to be an important modulator involved in the immunosuppression of sepsis,[24] suggesting a potential role of circMAN2B2 in sepsis-related immunosuppression. miRNAs are able to suppress ZEB1/2-mediated drug resistance and immunosuppression; therefore, circRNAs as upstream modulators of the miR/ZEB1 axis could have a possible role in sepsis-induced immunosuppression.[25]circMET was found to drive immunosuppression in hepatic carcinoma via the miR-30-5p/zinc finger protein SNAI1 (Snail) axis,[26] while Snail was markedly elevated in glomerular tissue in septic patients,[27] suggesting potential roles of circMET's in sepsis-related immunosuppression.

circRNAs in sepsis-related coagulation dysfunction

Activation of the coagulation system is affected during sepsis, which is a critical indicator during the development of sepsis. Endothelial cells (ECs) exert an essential effect on maintaining vascular homeostasis and are the primary targets of inflammatory mediators in sepsis. The persistent damage to ECs could cause organ failure.[28] A recent study showed that the overexpression of circ-C3P1 suppressed cell apoptosis and pro-inflammatory cytokines in pulmonary microvascular ECs in an LPS-induced sepsis mouse model by negatively modulating miR-21.[29] These findings indicate that the endothelial function could be damaged by the abnormal expression level of circRNAs, which finally leads to coagulation disorder and expedited septic progression.

circRNAs and sepsis-related organ dysfunction

circRNAs in sepsis-induced AKI

AKI is a frequently observed condition in the clinic with a high incidence rate, and acute inflammation and tissue injury are common indications. Sepsis is one of the most common causes of AKI, accounting for more than half of AKI cases. Among them, sepsis, triggered by LPS, is the dominant factor of AKI in patients in a critical condition, and is often used to establish in vitro sepsis-induced AKI models. Recently, a range of circRNAs have been shown to be involved in the development of AKI. For example, knockdown of circ-FANCA was found to alleviate LPS-induced HK2 cell injury by modulating the miR-93-5p/OXSR1 axis in sepsis-induced AKI.[30] circ-Ttc3 was found to reduce the inflammatory response and oxidation by targeting the miR-148a/Rcan2 axis in rats with sepsis-induced AKI, indicating that circ-Ttc3 could be a potential therapeutic target.[31] In addition, the involvement of circRNAs in regulating programmed cell death and cell cycle progression indicates that they are novel modulators for sepsis-induced AKI.[20] For example, circRar1 was found to induce the transcriptional activity of apoptosis-related factors in lead-induced neurotoxicity by regulating miR-671.[32]

circRNAs in sepsis-related acute respiratory distress syndrome

Acute respiratory distress syndrome (ARDS) is known as an independent risk factor for mortality in patients with sepsis. Accumulating evidence has shown that LPS can induce the activation and migration of the monocyte-macrophage system. This system further engulfs inflammatory particles invading the lungs, and secretes a mass of bioactive substances that facilitate neutrophil migration during ARDS development.[33] A recent study investigated the circ-ANKRD36-associated molecular mechanism underlying sepsis-related ARDS and confirmed that circ-ANKRD36 expression levels were markedly increased in the serum of patients with sepsis-related ARDS. In addition, knockdown of circ-ANKRD36 expression reduced cell viability and migration in LPS-treated RAW264.7 cells by sponging miR-330, suggesting a novel strategy in treating sepsis-related ARDS.[34] Another study confirmed the protective roles of the P2X7R antagonist in mice with sepsis-related

ARDS by regulating the expression levels of circ_0001679 and circ_0001212, suggesting these 2 circRNAs could be potential targets for sepsis-related ARDS treatment.[35]

circRNAs in sepsis-related myocardial dysfunction

Sepsis-related myocardial dysfunction (SIMD) is another significant complication following sepsis. Myocardial depressant factors, apoptosis, inflammatory cytokines, complement activation as well as nitric oxide have been found to contribute to the pathological course of SIMD.[36] The current strategies to treat SIMD include maintaining the stability of haemodynamics and supporting the normal cardiac function. Nevertheless, specific medications were limited, due to the undefined regulatory mechanism underlying the pathogenesis of SIMD. circRNAs are emerging as important modulators in a range of biophysiological processes, including myocardial dysfunction. For example, circ-HIPK2 was found to regulate proliferation and differentiation during myogenesis by targeting ribosomal protein Rpl7.[37] circACSL1 was found to modulate MAPK14 expression by sponging miR-8055 and aggravating myocardial inflammation and damage. This effect suggests that circACSL1 could be an effective biomarker used in the diagnosis and treatment of myocardial dysfunction.[38] In addition, miR-23b-induced activation of myocardial fibrosis has been confirmed as a key factor of myocardial dysfunction in advanced sepsis, while a miR-23b inhibitor was found to reduce cardiac fibrosis during the late stage of sepsis. A recent study found that the inhibition of miR-23b by circ_0005075 prevented polymicrobial sepsis-induced cardiac disorder by modulating TG-interacting factor 1 (TGIF1), phosphatase and tensin homologue deleted on chromosome 10 (PTEN), suggesting that circ_0005075 might be an effective modulator in the treatment of SIMD.[39] Recent studies on the roles of circRNAs in sepsis-induced organ failure are shown in Table 1.

circRNAs in virus-induced sepsis

Sepsis is commonly induced by bacterial infection; however, it can also be triggered by viral or fungal infection, causing weaker inflammatory responses. Until now, there is no definite diagnostic criterion for virus-induced sepsis. The discovery of circRNAs shows their advantages over other biomarkers, such as a high stability in the presence of viral infection, and may thus be used as potential diagnostic tools. A recent study found that NF90/NF110 released from host circRNP complexes could couple with viral mRNAs as part of the anti-viral immune response and against viral infection.[55] As circRNA expression is generally low, a certain group of circRNAs, not a single specific circRNA, may function together as molecular reservoirs of NF90/NF110 for rapid immune response upon viral infection.[55]

Technologies used to identify and evaluate circRNAs as biomarkers

The difficulty in distinguishing circRNAs from other non-coding RNAs has led to the late discovery of circRNAs. Currently, subject to the limited detection methods, circRNAs have to lose its circularity in order to be successfully detected. A protocol called Circle-Sequencing (Circle-Seq) has been recently proposed and used to process linear RNAs using RNase R enzyme, while keeping circRNAs intact.[56] However, this protocol shows certain limitation in determining the circularity of a RNA transcript as certain circRNAs are sensitive to RNase R, and might lead to false negative results. Other strategies, including 2-dimensional denaturing polyacrylamide gel electrophoresis, ribosomal RNA or poly(A) depletion, are also used to isolate and concentrate circRNAs in samples with unknown efficacy in clinical practice.[57] Microarray is another promising diagnostic tool, which can be used to determine the relative levels of different circRNAs due to its sensitivity and specificity. However, it is only able to evaluate those circRNAs covered in the array, and cannot be used to measure the total amount of circRNAs.[58]

Currently, reverse transcription-quantitative polymerase chain reaction is broadly utilised to recognise and quantify circRNAs. It shows great advantages over other methods as it is simple and inexpensive as a detection tool for diagnostic biomarkers.[59] In addition, RNA-sequencing (RNA-Seq) technology, combined with bioinformatics analysis, enables the comprehensive study on circRNAs, and significantly contributes to the discovery and characterisation of circRNAs.[60] Disease-related circRNAs have been identified in human peripheral blood using RNA-Seq.[45]

circRNAs have a crucial role in sepsis, thus it is essential to clarify the underlying mechanisms of different circRNAs involved in the pathogenesis of sepsis, in addition to identifying novel circRNAs that regulate the heterogeneity of sepsis.

CONCLUSION

Diagnosis of early sepsis is extremely important to maximise the survival rate in patients with sepsis. The availability of accurate biomarkers will be particularly beneficial to enable the delivery of prompt and appropriate treatment. However, none of the current biomarkers, that are clinically evaluated could offer 100% specificity for the diagnosis of sepsis.[4] circRNAs, as newly identified

Table 1. Recent studies on the roles of circRNAs in sepsis-induced organ failure

circRNAs	Downstream targets	Functions
circ-ANKRD36	miR-330	Its knockdown suppresses cell viability and migration in LPS-stimulated cells[34]
circ-BNIP3L	miR-370-3p/MYD88	Its knockdown alleviates LPS-induced renal tubular epithelial cell injury[40]
circ-C3P1	miR-21	Attenuates pro-inflammatory cytokine production and cell apoptosis in septic ALI[29]
circ-DMNT3B	miR-20b-5p	Its downregulation is conducive to intestinal mucosal permeability dysfunction[41]
circ-FADS2	miR-15a-5p	Suppresses LPS-induced lung cell apoptosis[42]
circ-FANCA	miR-93-5p/OXSR1	Its knockdown alleviates LPS-induced HK2 cell injury[30]
circ-Fryl	miR-490-3p/SIRT3	Attenuates sepsis-induced lung injury[43]
circ-HIPK3	miR-29b	Promotes homeostasis of the intestinal epithelium[44]
circ-PRKCI	miR-545	Associated with sepsis risk, disease severity and 28-day mortality[45]
	miR-545/ZEB2	Relieves LPS-induced HK2 cell injury[46]
	miR-106b-5p/GAB1	Alleviates LPS-induced HK2 cell injury[47]
circ-PTK2	miR-181c-5p/HMGB1	Regulates microglia activation and hippocampal neuronal apoptosis induced by sepsis[48]
circ-TLK1	miR-106a-5p/HMGB1	Promotes sepsis-associated AKI by regulating inflammation and oxidative stress[49]
circ-Ttc3	miR-148a/Rcan2	Regulates inflammation and oxidative stress in septic rats with AKI[31]
circ-VMA21	miR-199a-5p/NRP1	Ameliorates LPS-induced AKI[50]
	miR-9-3p/SMG1	Ameliorates sepsis-associated AKI inflammation and oxidative stress[51]
circ_0001105	YAP1	Protects intestinal barrier in septic rats by inhibiting inflammation and oxidative damage[22]
circ_0003420	NPAS4	Mediates inflammation in sepsis-induced liver damage[20]
circ_0068,888	miR-21-5p	Protects against LPS-induced HK2 cell injury[21]
circ_0091702	miR-545-3p/THBS2	Attenuates sepsis-related AKI[52]
	miR-182/PDE7A	Relieves LPS-induced cell injury[53]
circ_0114428	miR-495-3p/CRBN	Regulates sepsis-induced kidney injury[19]
circ_104484/circ_104670	-	Serves as potential novel biomarkers and therapeutic targets for sepsis[54]

AKI: acute kidney injury; ALI: acute lung injury; circ/circRNA: circular RNA; CRBN: cereblon; GAB1: growth factor receptor binding 2-associated binding protein 1; HK2: human kidney 2; HMGB1: high mobility group box 1; LPS: lipopolysaccharide; miR: microRNA; MYD88: myeloid differentiation primary response protein 88; NPAS4: neuronal PAS domain protein 4; NRP1: neuropilin-1; OXSR1: oxidative stress-responsive 1; PDE7A: phosphodiesterase 7A; Rcan2: regulator of calcineurin 2; SIRT3: sirtuin 3; SMG1: suppressor of morphogenesis in genitalia 1; THBS2: thrombospondin 2; YAP1: Yes-associated protein 1; ZEB2: zinc finger E-box binding homeobox 2

Superscript numbers: Refer to numbers in REFERENCES

non-coding RNAs, have been associated with various molecular responses such as inflammation, immune suppression and endothelial function, and are significantly altered during the progression of sepsis.

circRNAs show promising potential as biomarkers based on their strong resistance to exonucleases and high stability in blood. Their levels are increased and have an average half-life of 48 hours compared to 10 hours for other linear non-coding RNAs in the serum.[61] The putative function of circRNAs as miRNA sponges makes them particularly interesting therapeutic targets for future research. Furthermore, circRNAs have tissue-specific and developmental stage-specific features. Their expression levels have been shown to be associated with the occurrence and development of various diseases, including sepsis. However, the understanding of circRNA-modulated sepsis-induced organ failure is still at a very early stage. Further research is urgently required to investigate the regulation of circRNAs in the progression of different diseases, and to identify specific circRNAs in certain diseases. Therefore, circRNAs are attracting increasing attention in sepsis research, and may play significant roles in the diagnosis, treatment and prognosis of sepsis.

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