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# Utilizing omics technologies in the investigation of sepsis-induced cardiomyopathy

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ABSTRACT

Sepsis-induced cardiomyopathy (SIC) is a common and high-mortality complication among critically ill patients. Uncertainties persist regarding the pathogenesis, pathophysiology, and diagnosis of SIC, underscoring the necessity to investigate potential biological mechanisms. With the rise of omics technologies, leveraging their high throughput and big data advantages, a systems biology perspective is employed to study the biological processes of SIC. This approach aids in gaining a better understanding of the disease's onset, progression, and outcomes, ultimately providing improved guidance for clinical practices. This review summarizes the currently applied omics technologies, omics studies related to SIC, and relevant omics databases.

## 1. Introduction

Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection [1]. Sepsis is one of the leading causes of mortality in the intensive care unit (ICU) [2]. Septic shock can be characterized as a subset of sepsis, in which significantly severe circulatory, cellular, and metabolic abnormalities are linked to a higher risk of mortality compared to sepsis without such profound abnormalities [1]. In adult septic shock patients, 60 % of patients can exhibit ventricular dysfunction and compromised overall heart function [3]. Numerous clinical studies have indicated that myocardial dysfunction is associated with an increased mortality rate in septic patients [4–6]. It is worth noting that due to the difficulty in obtaining human cardiac samples, rodents (*rats* and *mice*) are commonly used animal models in the study of sepsis and sepsis-related organ damage mechanisms, given their biological similarities to humans in many processes such as immune response, metabolic pathways, and neural functions. Li and coworkers demonstrated through *mouse* studies that the activation of the cardiac-specific PI3K/Akt signaling pathway can notably reduce the occurrence and mortality rates associated with septic shock [7]. This finding represents the initial evidence establishing a direct link between the preservation of myocardial function and the survival of individuals with sepsis. Therefore, a thorough investigation of the pathogenesis of Sepsis-induced cardiomyopathy (SIC) and its disease progression is crucial for improving the prognosis of sepsis. In recent years, omics research, including genomics, transcriptomics, proteomics, and metabolomics, has made advancements in the study of SIC, aiding in the comprehension of its intricate molecular mechanisms and biological processes. This review aims to provide an overview of the applications of omics research in SIC and its prospects.

Despite its significant clinical impact, SIC currently lacks a unified definition, and there are discrepancies in its incidence, prognosis, and clinical significance, emphasizing the diversity of its underlying biological mechanisms. A series of omics technologies have emerged, where "omics" refers to the comprehensive study of various types of molecules within cells and their interactions. It started with genomics, with new sequencing technologies enabling rapid decoding of entire genomes and the study of all genes. This also includes transcriptomics (the study of gene expression in cells or organisms), proteomics (the analysis of all proteins), metabolomics (comprehensive analysis of small molecules),

*Abbreviations:* **ICU**, **intensive care unit**; **SIC**, **Sepsis-induced cardiomyopathy**; **LPS**, **ipopolysaccharide**; **CLP**, **cecal ligation and puncture**; **MCTR1**, **maresin conjugates in tissue regeneration 1**; **IRHG**, **immune-related highly expressed gene**; **GEO**, **Gene Expression Omnibus**; **2-DGE**, **Two-Dimensional Gel Electrophoresis**; **LC-MS**, **Liquid Chromatography-Mass Spectrometry**; **MS**, **Mass spectrometry**; **GO**, **Gene Ontology**; **KEGG**, **Kyoto Encyclopedia of Genes and Genomes**; **MeRIP-Seq**, **methylated RNA immunoprecipitation sequencing**; **H9c2**, **myocardial cells**; **GC–MS**, **gas chromatography-mass spectrometry**; **NMR**, **Nuclear Magnetic Resonance**; **AI**, **astragalus injection**; **CY**, **Chinese yam**; **Ade**, **adenosine**; **Arb**, **arbutin**; **All**, **Allantoin**; **PCA**, **principal component analysis**; **a cell-permeable Beclin-1 activating peptide**, **TB-peptide**; **Sirt3**, **Sirtuin 3**; **VDAC2**, **Voltage-Dependent Anion Channel 2**.

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and epigenomics (the study of epigenetic regulation of the entire genome). [8] Omics technology aims to analyse the overall structure and function of organisms rather than focusing on the analysis of individual genes or pathways. By leveraging the advantages of high-throughput technologies, it can generate large volumes of data, uncover complex regulatory networks, and identify potential biomarkers within organisms. The ultimate goal is to elucidate the molecular mechanisms of SIC, improve its diagnosis, and develop more effective treatment strategies. Therefore, we will discuss the application of individual omics technologies in the research of SIC.

## 2. Omic studies of SIC

Omic technologies are shifting their focus from individual molecules or pathways to the holistic analysis of biological systems. This involves integrating functional experiments to comprehensively understand molecular mechanisms. The ultimate goal is to comprehensively understand disease mechanisms, discover new biomarkers, uncover potential therapeutic targets, and develop disease-specific treatments for patients with SIC(Fig. 1).

Therefore, we will first discuss the application of individual omics technologies in SIC research (Table 1), followed by a comprehensive application of multi-omics.

## 3. Genomics

The term “genomics” was coined over 30 years ago, at the inception of the Human Genome Project. It aims to investigate individual genetic variations, including single nucleotide polymorphisms and copy number variations, that render susceptibility to specific diseases or conditions. There are currently three main approaches to pursue genomic studies: ( 1 ) Whole genome sequencing achieves comprehensive detection of various types of common and rare genetic variations across almost the entire genome, enabling the creation of high-quality genomic variation profiles for the samples of interest. [9] ( 2 ) Whole exome sequencing helps identify genetic variations within an individual’s protein-coding sequences, offering a faster and more cost-effective technique. ( 3 ) DNA microarrays are molecular biology tools that take advantage of the distinctive property of single-stranded DNA to bind with complementary DNA sequences, enabling the specific recognition of DNA sequences. [10].

So far, no relevant studies have been identified that have utilized large-scale genomics approaches to identify genetic variations associated with SIC. Currently, genomic research is widely applied in areas such as cancer and genetic diseases, utilizing big data and high-throughput techniques to identify genetic mutations and their impact on diseases. SIC fundamentally stems from changes in the external environment rather than internal mutations. Moreover, there are complex and variable processes involving transcription, translation, and post-translational modifications between genetic changes at the molecular level and the actual pathological and physiological alterations that occur. Additionally, the relatively high cost of genomic technologies is a factor contributing to their limited application in this field. Another limitation is the large number of patients required, given the small effect size of individual genetic variations, as well as the difficulty in defining an appropriate control group. These factors may explain the limited utilization of genomics in the field of SIC. In the future, genomic research on SIC may be conducted to identify the genetic determinants of the disease and generate new mechanistic hypotheses, exploring additional potential mechanisms to assist in the development of improved clinical treatment strategies.

## 4. Transcriptomics

The transcriptome is a comprehensive collection of gene transcripts or RNA species transcribed in response to specific physiological or pathological conditions within cells or tissues. It encompasses both coding RNAs and non-coding RNAs, with the latter involved in post-transcriptional regulation, thereby influencing gene expression. Transcriptomics focuses on the transcription process of genes and involves comparing cells or tissues under specific conditions or different states to identify changes in gene expression. [11] Currently, there are several common transcriptional sequencing methods (1) Microarrays: This is an early transcriptomics method that uses DNA probes to capture RNA molecules, followed by detection using fluorescence or other methods to measure RNA expression levels. (2) RNA-Seq: This is one of the most commonly used transcriptomics sequencing methods. It involves transcribing RNA molecules into complementary DNA (cDNA) and then conducting high-throughput sequencing to detect and quantify the expression levels of different genes. (3) Single-Cell RNA Sequencing (scRNA-Seq): This method allows for the analysis of gene expression at the single-cell level, revealing differences between different cell types and states. It can be applied to research in various areas, including development, tissue diversity, and tumor cell heterogeneity.

Matkovich et al. utilized microarray technology and found that, in the myocardial tissues of patients with SIC, most of the changes in mRNA

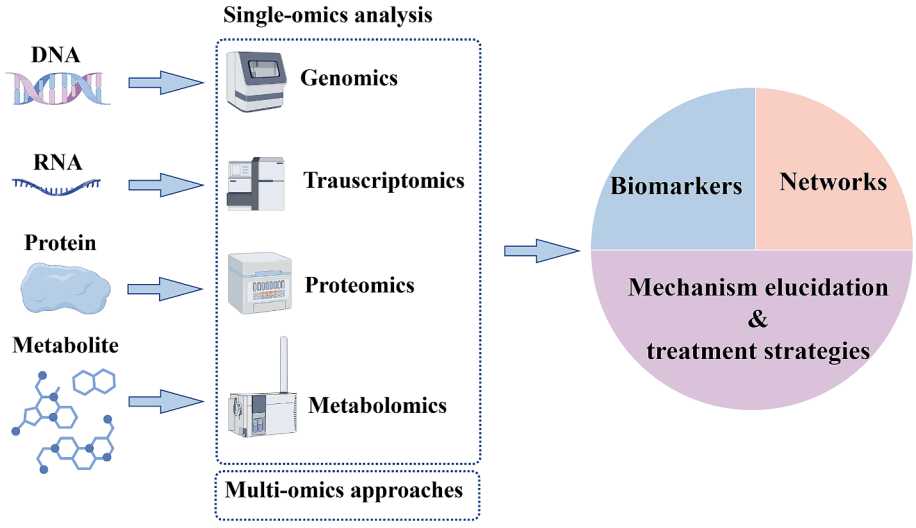


**Fig. 1.** Schematic diagram of multi-omics approaches for SIC.Single omics data can be integrated into multi-omics and used in systems biology to study the pathophysiological mechanisms of SIC and the discovery of biomarkers, thereby improving therapeutic strategies.

**Table 1**
Summary of omics studies of SIC.

| Study | Omic technology | Methods/models | Major finding |
|---|---|---|---|
| Santos,2010 [31] | Transcriptomics, RNA Microarray | *Mouse* CLP sepsis | iNOS may alter the gene expression in the central heart during SIC by regulating PGC-1, including decreased expression of contractile proteins, growth-related genes, and energy-producing genes. |
| Wang,2014 [15] | Transcriptomics, RNA Microarray | *Mouse* CLP sepsis | The deficiency of miR-223/–223* exacerbates local and systemic inflammation by targeting STAT3/IL-6 and Sema 3A, leading to severe myocardial suppression during the critical stage of sepsis. |
| Matkovich,2016 [12] | Transcriptomics, RNA Microarray | 20 sepsis patients, 11 IHD, 9 DCM, 11 non-failing donors. | Most of the changes in mRNA expression levels observed in SIC patients are different from those in heart failure. |
| Tran,2019 [32] | Transcriptomics, RNA Microarray | *Rat* CLP sepsis | In SIC, there are gender differences in the response to landiolol, with gender-specific variations observed in the gene transcription levels of the β-adrenergic signaling pathway and calcium cycling pathway. |
| Chen,2020 [33] | Transcriptomics, RNA Sequencing | *Mouse* after intraperitoneal injection of LPS | LPS inhibits the Wnt signaling pathway, inducing cardiac damage, and the Wnt signaling plays a crucial role in the development of sepsis. |
| Ektesabi,2021 [34] | Transcriptomics, RNA Microarray | *Mouse* CLP sepsis | The cardioprotective effect of Mesenchymal Stem Cell (MSC) therapy in sepsis may be associated with the regulation of miR-187 and its interaction with target genes. |
| Yang,2021 [14] | Transcriptomics, RNA Sequencing | *Mouse* after intraperitoneal injection of LPS | MCTR1 can reduce the levels of neutrophil chemotactic factors, alleviating neutrophil infiltration. MCTR1 also inhibits the production of IL-17A in γδT cells, protecting cardiac function in SIC. |
| Zhou,2022 [35] | Transcriptomics, RNA Sequencing | *Human* serum samples, *Mouse* CLP sepsis and *Mouse* after intraperitoneal injection of LPS | In SIC, the H2S donor GYY4137 primarily regulates the inflammatory response pathway through the NLRP3 pathway, inhibiting inflammation and protecting the myocardium. |
| Liu,2022 [36] | Transcriptomics, RNA Sequencing | *Mouse* after intraperitoneal injection of LPS | LCN-2 may be involved in severe septic myocardial injury and associated with lipid metabolism disruption and mitochondrial dysfunction. |
| Liu,2022 [13] | Transcriptomics, RNA Sequencing | Analysis from multiple databases | Melatonin has a pronounced cardioprotective effect on septic myocardial injury by inhibiting the PIK3CG-related signaling pathway. |
| Yuan,2022 [37] | Transcriptomics, RNA Microarray | *Mouse* CLP sepsis | 158 tsRNAs showed significant changes in SIC, and these tsRNAs may play a protective role in the occurrence and development of SIC. |
| Du,2022 [38] | Transcriptomics, RNA Sequencing | *Mouse* after intraperitoneal injection of LPS | In the heart tissue of *mice* in the SIC group, genes related to the necrotic pathway were significantly enriched, and 35 differentially expressed genes (NRDEGs) related to necrosis were identified, including MLKL and RIPK3. |
| Zou,2022 [30] | Transcriptomics, RNA Microarray | Analysis from database | In SIC, there is widespread dysregulation of autophagy-related genes. |
| Yang,2022 [39] | Transcriptomics, Single-Cell mRNA Sequencing | *Mouse* CLP sepsis | Low-level tragus stimulation can promote the transformation of monocytes in the myocardium into M2 macrophages, possibly through the activation of the cholinergic anti-inflammatory pathway, thereby improving SIC. |
| Yan,2022 [40] | Transcriptomics, RNA Sequencing | *Mouse* CLP sepsis | At 24, 48, and 72 h in the CLP group, DEGs related to processes such as cell adhesion, immune system processes, and inflammatory responses were identified. Among them, 15 expression profiles showed significant differences, and Pik3r5 may play a role in regulating the progression of SIC. |
| Li,2022 [16] | Transcriptomics, miRNA microarray | Analysis from database | The immune-related regulatory network miR-222-3p/THBS1 may be involved in the pathogenesis of SIC, and THBS1 could be a key biomarker for the diagnosis of SIC. |
| Zou,2023 [41] | Transcriptomics, RNA Microarray | Analysis from database | In SIC, there is a widespread dysregulation of ferroptosis-related genes (FRGs). Eight key FRGs regulating ferroptosis were identified in the SIC, along with their characteristics related to ferroptosis. |
| Zou,2023 [42] | Transcriptomics, | Analysis from database and *Mouse* CLP sepsis | Hmgcs2 inhibits the activation of pro-inflammatory macrophages and protects against SIC injury by activating the PI3K/Akt pathway in a src-dependent manner. |
| Zheng,2023 [43] | Transcriptomics, RNA Microarray | *Mouse* after intraperitoneal injection of LPS | In the LPS-treated group, a total of 1735 differentially expressed circular RNAs were identified, comprising 990 upregulated and 745 downregulated circular RNAs. Among them, 309 mRNAs and 187 circular RNAs were associated with autophagy in myocardial tissue after SIC. |
| Ullah,2023 [44] | Transcriptomics, RNA Sequencing | *Mouse* CLP sepsis and *mouse* after intraperitoneal injection of LPS | The CLP and LPS methods can induce SIC within 24 h. Compared to the control group, DEGs are involved in shared pathways, including regulation of inflammatory response, modulation of reactive oxygen metabolism processes, and the JAK-STAT signaling pathway. |
| Hinkelbein,2010 [18] | Proteomics,2D-GE and MS | *Rat* CLP sepsis | The pathophysiological mechanism of SIC is demonstrated to involve impaired mitochondrial function due to the dysregulation of key enzymes in the tricarboxylic acid cycle. |
| Shimada,2022 [19] | Proteomics, MS | *Mouse* CLP sepsis | The mitochondrial protein PDK4, the main kinase responsible for phosphorylation and inactivation of PDH (pyruvate dehydrogenase), is upregulated in SIC, leading to a significant decrease in PDH activity. |
| Yang,2022 [20] | Proteomics, LC-MS | *Rat* CLP sepsis | Acetylated lysine, succinylated lysine, and 2-hydroxyisobutyrylated lysine modifications are significantly decreased in the heart tissue of the sepsis group. |
| Zhou,2018 [23] | Metabolomics, UPLC-Q-TOF-MS | *Rat* after intraperitoneal injection of LPS | CY (Chinese yam) and its three bioactive components (Ade, Arb, and All) can improve SIC and are involved in five metabolic pathways: amino acid metabolism, arachidonic acid metabolism, sphingolipid metabolism, sugar metabolism, and glycerophospholipid metabolism. |
| Liang,2019 [45] | Metabolomics, UPLC-Q-TOF-MS | *Mouse* after intraperitoneal injection of LPS | In SIC, a total of 21 differential metabolites were identified, involving biosynthesis of phenylalanine, tyrosine, and tryptophan, arachidonic acid metabolism, glycine, serine, and threonine metabolism, etc. |

(*continued on next page*)

**Table 1** (*continued*)

| Study | Omic technology | Methods/models | Major finding |
|---|---|---|---|
| Lin,2020 [46] | Metabolomics, GC–MS /MS | Plasma samples from 31 patients with sepsis | The alterations in relevant metabolites in SIC, such as the upregulation of glutamine, and their positive correlation with CK-MB, provide clinical evidence for the energy metabolism mechanism of SIC. |
| Kim,2022 [24] | Metabolomics, LC–MS | *Mouse* after intraperitoneal injection of LPS | The activation of autophagy leads to an increase in lactate levels in cardiac tissue, concurrently affecting the levels of various metabolites, including fatty acids, amino acids, and glucose metabolism products. |
| Wang,2023 [47] | Metabolomics, LC–MS | *Rat* CLP sepsis and *rat* after intraperitoneal injection of LPS | The UTMD technique and melatonin treatment for heart-derived ROR improved mitochondrial dysfunction and adrenergic distribution. |
| Jiang,2023 [25] | Metabolomics, LC–MS | *Mouse* after intraperitoneal injection of LPS | NSC228155 corrects oxidative stress and energy metabolism disruption in the cardiac tissue, especially in the AA-related pathway, in the LPS model. |

expression levels are distinct from those observed in heart failure patients [12]. While the specific reasons for these differences are unclear, they may be related to variations in the cardiac transcriptional profile observed during acute and chronic cardiac injury, as well as to fundamental differences in the pathological mechanisms of sepsis and heart failure. These findings underscore the dynamicity and specificity of gene expression across different disease states. Liu et al. conducted transcriptome analysis using RNA sequencing on cecal ligation and puncture (CLP) and sham *mice* [13]. Subsequently, they employed bioinformatics to identify PIK3CG as a crucial target. Experimental validation confirmed that inhibiting the PIK3CG-related signaling pathway (The PI3K signaling pathway belongs to the intracellular signaling pathways, regulating various cellular physiological processes such as proliferation, differentiation, migration, and metabolism.) has a pronounced cardioprotective effect on septic myocardial injury, revealing the critical role of PI3K family members in sepsis. Yang et al. conducted a transcriptome analysis based on RNA sequencing of isolated RNA from myocardial tissues in the LPS group (*mice* intraperitoneally injected with LPS) and the LPS+maresin conjugates in tissue regeneration 1 (MCTR1) group (*mice* intraperitoneally injected with LPS followed by intravenous injection of MCTR1 via the tail vein 6 h later) [14]. They confirmed that MCTR1 can reduce the levels of neutrophil chemotactic factors, alleviating neutrophil infiltration. MCTR1 also protects cardiac function in SIC by inhibiting the production of γδT cell IL-17A. Therefore, MCTR1 may represent a novel therapeutic strategy for SIC. Wang et al. used a miRNA array analysis, for the first time, to investigate the expression patterns of myocardial miRNAs following severe sepsis in a *mouse* model of CLP [15]. They observed a significant downregulation of miR-223/–223* in the hearts of *mice* after severe CLP surgery, indicating that the reduction of miR-223/–223* might be a primary contributor to the multi-organ dysfunction and mortality induced by sepsis. Future studies need to clarify whether miR-223/–223* would be optimal therapeutic agents to treat sepsis. Li et al. analyzed three *human* and *mouse* SIC datasets from the Gene Expression Omnibus (GEO) database and identified THBS1 as a potential key immune-related highly expressed gene (IRHG). [16] Furthermore, an immune-related regulatory network involving miR-222-3p/THBS1 may be involved in the pathogenesis of SIC. It's important to note that this study has not yet been validated in animal models.This study reveals the importance of immune regulation in septic myocardial injury, providing clues for further research on the role of immune regulation in disease treatment. Transcriptomics provides a more intuitive way to capture changes in RNA expression levels. By comparing transcript information between control and experimental groups, researchers can identify changes in the expression of disease-specific genes and relevant RNAs influencing disease occurrence. This aids in understanding interactions between genes and potentially involved regulatory networks, providing new avenues for research.

## 5. Proteomics

Proteomics focuses on information related to protein levels in organisms. Unlike genomics, proteomics, is dynamic, varying with cell type and functional state, encompassing the study of all expressed protein functions. Conducting proteomic analysis contributes to our understanding of the molecular bases associated with the identification of cell signaling, protein modification, and post-translational modification pathways. Researches predominantly utilize two proteomics methods: (1) Two-Dimensional Gel Electrophoresis (2-DGE): 2-DGE is a traditional method for protein separation, but it has several limitations, such as being time-consuming, costly, and less sensitive to low-abundance proteins. (2) Liquid Chromatography-Mass Spectrometry (LC-MS): Mass spectrometry (MS) is one of the most commonly used methods in proteomics. It is more sensitive to low-abundance proteins, improves peptide identification coverage, and offers higher detection sensitivity, enabling precise protein quantification. [17].

Hinkelbein et al. conducted two-dimensional gel electrophoresis on the hearts of *rats* from the CLP group and the sham group [18]. Over 1100 proteins were identified, with 12 proteins significantly regulated in the heart. Approximately 82 % of cardiac proteins were associated with mitochondrial function. The protein profile in the heart underwent significant changes at 12, 24, and 48 h after sepsis induction. Shimada et al. conducted proteomic analysis of isolated heart mitochondria from severely heart-failing *mice* and CLP *mice* using LC-MS [19]. Among 665 mitochondria-associated proteins, they discovered significant differences in 35 mitochondrial-related proteins involved in various bioenergetic functions between sham and CLP mitochondria. Both of the above studies identified through proteomic analysis that mitochondrial-related proteins or functions in SIC have an impact on the disease, providing insights for further exploration into the pathogenesis of mitochondrial-related SIC. Yang et al. conducted a quantitative analysis of the global proteome of left ventricular tissues from 16 *rats* (8 in the sepsis group and 8 in the control group) using LC-MS technology [20]. They identified 108 differentially expressed (DE) proteins. Further bioinformatics analysis revealed that these DE proteins played significant roles in metabolic and immune-related processes and pathways. In SIC depression *rats*, acetyllysine, succinyllysine, and 2-hydroxyisobutyryllysine modifications in cardiac tissues were significantly reduced. Additionally, lactyllysine modifications in the whole proteome significantly increased in certain specific-weight proteins, while it significantly decreased in other proteins. This study demonstrated the substantial differences in protein post-translational modifications between the two groups, highlighting the impact of post-translational modifications on proteins. Proteomic analysis identified multiple differentially expressed proteins, and bioinformatics analyses such as Gene Ontology(GO) and Kyoto Encyclopedia of Genes and Genomes(KEGG) were employed to investigate the disruption of cellular signaling pathways and metabolic pathways in SIC injury. This provides a molecular foundation for exploring the mechanisms underlying the cardiac dysfunction induced by sepsis.

## 6. Epigenomics

Epigenetics is the study of changes in gene activity and inherited traits that do not involve alterations to the DNA sequence itself. It focuses on how chemical modifications and other molecular mechanisms impact gene expression and the transmission of genetic features during

cell division and the process of genetic inheritance. Epigenetic research encompasses various elements, including DNA methylation, histone modifications, non-coding RNA, chromatin structure, and parental effects.

Xie et al. used RNA m6A dot blot to detect elevated m6A levels in the *mouse* myocardial tissues of the LPS group compared to the control group and identified YTHDC1 as the primary upregulated m6A reader protein. [21] Through GEO database analysis, SERPINA3N was found to be significantly upregulated in septic *mouse* and rat myocardial tissues. Using knockout methods, it was confirmed that YTHDC1 regulates the inflammatory response of SIC through m6A modification in SERPINA3N transcripts. Shen et al. conducted methylated RNA immunoprecipitation sequencing (MeRIP-Seq) on myocardial cells (H9c2) induced by lipopolysaccharide (LPS) at a concentration of 10 μg/mL [22]. The research results revealed the m6A profile of the septic myocardial injury cell model, indicating that m6A modifications (including 3′-UTR, 5′-UTR, and CDS) were distributed in myocardial cells after myocardial injury. Further investigation identified significant m6A modification sites on the 3′-UTR of the HDAC4 gene as downstream targets of METTL3. Additionally, the m6A reader IGF2BP1 was found to recognize m6A modification sites on HDAC4 mRNA, enhancing its RNA stability (The m6A modification can enhance the stability of RNA, prolonging the lifespan of RNA molecules within cells and slowing down their degradation rate. This modification contributes to ensuring the sustained expression of specific genes in the cell.). Both of these studies explored the role of m6A modification in SIC, suggesting that further investigation into the molecular mechanisms of m6A modification in the onset and progression of the disease, and its regulatory effects on gene expression and cellular function, may contribute to a deeper understanding of the pathogenesis of SIC. Epigenomic analysis can reveal the levels and distribution of modifications on DNA or RNA, investigating how gene expression and functionality are regulated or contribute to various biological processes.

## 7. Metabolomics

Metabolomics involves the thorough and systematic identification, and quantitative analysis, of molecules with a molecular weight below 1000 Daltons in biological samples like blood and tissues. This analysis is conducted under various physiological or pathological conditions. Metabolites are the ultimate products of biological activity and serve as direct and comprehensive biomarkers of physiological phenotypes, making metabolomics a focus of biomarker discovery research. Metabolomics commonly employs the following two techniques: (1) Mass Spectrometry (MS): Mass spectrometry is one of the most commonly used techniques in metabolomics. It analyzes the mass spectrometric characteristics of metabolites in biological samples, including molecular weight, fragmentation patterns, and relative abundances. Different mass spectrometry techniques, such as gas chromatography-mass spectrometry (GC–MS) and liquid chromatography-mass spectrometry (LC-MS), can be selected based on the specific research objectives. (2) Nuclear Magnetic Resonance (NMR): NMR technology determines the structure and concentration of metabolites by analyzing the nuclear magnetic resonance spectra of these molecules. While NMR is less sensitive compared to mass spectrometry, it offers advantages such as multidimensional information, non-destructiveness, quantitative capabilities, and the ability to analyze metabolites without the need for sample separation.

Zhou et al. conducted a metabolomics analysis of seven groups (control group, SIC model group, astragalus injection (AI) treated group, Chinese yam (CY) extract treated group, adenosine (Ade) treated group, arbutin (Arb) treated group, and allantoin (All) treated group of *rats* using UPLC-Q-TOF-MS [23]. Through principal component analysis (PCA) and correlation network analysis, they found that CY/Ade/Arb/All were involved in five metabolic pathways, including amino acid metabolism, arachidonic acid metabolism, sphingolipid metabolism, carbohydrate metabolism, and glycerophospholipid metabolism, significantly improving SIC. Kim et al. performed targeted metabolomics analysis using LC-MS technology on heart tissue samples collected from both young and aged *mice* exposed to lipopolysaccharide challenge or sham treatment, followed by subsequent administration of TB-peptide (a cell-permeable Beclin-1 activating peptide) or vehicle [24]. The study revealed that TB-peptide has a beneficial effect on the glucose and amino acid metabolism damage induced by LPS in both young and aged *mice*. However, regarding the regulation of lipid metabolism, age-dependent variations were observed. Specifically, TB-peptide demonstrated a significant improvement in lipid metabolism damage in young *mice*, while its impact was less pronounced in aged *mice*. The research demonstrates the cardioprotective effect of TB-peptide through pharmacological activation of Beclin-1. Jiang et al. conducted non-targeted metabolomics analysis on myocardial tissues of *mice* in LPS models, with or without NSC228155 (2-[(7-nitrobenzo[c]oxadiazol-4-yl)thio] pyridine 1-oxide is a novel compound with multiple therapeutic potential against cancer, toxicity of pertussis toxin, and acute kidney injury) [25]. They observed a significant reduction in ten differentially expressed metabolites in the NSC228155 group. Metabolomics analysis indicated that NSC228155 could ameliorate oxidative stress and metabolic disruptions, particularly in the AA-related pathways in myocardial tissues. These findings suggest that NSC228155 may have a protective role in mitochondria, suppress inflammation, and consequently alleviate LPS-induced myocardial damage.

Metabolomics analysis assists in identifying metabolic pathways associated with relevant drugs and evaluating the therapeutic effects of drugs on SIC. It can also be utilized to analyze differential metabolites and the biological pathways they are involved in, further exploring the pathogenesis, diagnosis, and treatment of SIC.

## 8. Multi-omics

Multi-omics is a systematic biology approach that comprehensively integrates molecular information from multiple levels to gain a holistic understanding of the molecular mechanisms within an organism. Depending on the requirements of the research design, data from various omics layers can be combined. For instance, if two omics elements are driven by the same factor or if one interferes with the other, they may exhibit simple correlations or synergistic effects, establishing associations. [26] While current omics research on SIC predominantly focuses on individual omics studies, there are also a few that integrate multiple omics technologies, such as the joint analysis of proteomics and metabolomics or the combined analysis of transcriptomics and metabolomics.

Xu et al. conducted proteomic and targeted metabolomics analyses on myocardial tissues from normal WT, septic WT, and septic Sirtuin 3 (Sirt3)−/− *mice* [27]. The combined analysis of proteomics and metabolomics data revealed that Sirt3 deficiency-mediated hyperacetylation of key enzymes in the cardiac TCA cycle may impede the compensatory response to sepsis-induced cardiac energy metabolic injury. Consequently, myocardial metabolism shifts from glucose oxidation to anaerobic glycolysis, leading to increased generation of lactate and NADH, ultimately exacerbating SIC. Jia et al. conducted non-targeted metabolomics and transcriptomics on *mice* from the LPS model group and the control group [28]. A combined analysis of metabolomics and transcriptomics data identified five differential metabolites (d-mannitol, d-glucosamine 6-phosphate, maltose, α-linolenic acid, and 5′-AMP). Furthermore, enrichment analysis using KEGG revealed pathways associated with differentially expressed metabolites and genes. She et al. conducted proteomics and targeted metabolomics on *mice* from the CLP group and the control group. [29] A combined analysis of the obtained omics data revealed that in SIC, there was an elevation in malonyl-CoA, inducing malonylation of Voltage-Dependent Anion Channel 2 (VDAC2), significantly impacting mitochondria-associated ferroptosis. In this study, the researchers established, for the first time,

an association between VDAC2 malonylation and ferroptosis, proposing a novel potential mechanism for SIC. Multi-omics analysis reveals significant changes in proteins and metabolites associated with SIC. The integration of various data types helps us establish new associations, providing new perspectives and possibilities for the diagnosis and treatment of SIC.

## 9. Omics databases

Omics databases serve as platforms for storing and managing a variety of omics data, providing valuable resources for researchers. These databases encompass rich information about biological molecules such as genes, proteins, metabolites, including aspects like sequences, structures, functions, and expression levels. Many omics databases follow an open-sharing model, enabling global scientists to freely access and utilize these data, fostering collaborative research. Databases not only provide convenient data services for many researchers but also help them save costs to some extent. This review summarizes commonly used omics databases (Table 2). For example, Liu et al. employed a method that involves searching databases for sepsis-related target genes and using transcriptomics to detect differentially expressed genes in CLP-injured *mice* [13]. This approach aims to jointly characterize targets associated with sepsis. Zou et al. utilized datasets from human samples to conduct relevant bioinformatic analyses and identified key genes, which were subsequently validated using the H9c2 cardiomyocyte cell line [30]. Li et al. conducted bioinformatic analyses using datasets from human and mouse heart samples. They identified an immune-related regulatory network, miR-222-3p/THBS1, which may be involved in the pathogenesis of SIC [16].

## 10. New techniques and future perspectives

The field of omics has been continually advancing, giving rise to numerous new technologies and evolving over time. For instance, single-cell technology enables researchers to perform gene expression, protein expression, and metabolite measurements at the individual cell level, revealing cellular heterogeneity and functional subpopulations. Spatial omics technologies allow for high-resolution molecular measurements at the tissue and cellular levels, uncovering interactions between different cells and molecular distributions. In the future, we anticipate the development of faster, high-throughput sequencing technologies, further propelling cutting-edge research in the life sciences and providing deeper insights into disease treatment, health management, and foundational biological research.

## 11. Conclusions

Although we have gained some understanding of the pathophysiology and biomarkers of SIC, this severe condition remains common and highly perilous. The advancement of omics research allows us to obtain a broader range of samples, including cardiac tissues, blood, and other physiological specimens, along with patient data, providing significant opportunities for in-depth exploration of SIC. With the decreasing cost of omics analyses and the emergence of novel omics technologies, and their integrated application, there has been a push for further research into the etiology, pathophysiology, and diagnosis of SIC, with the prospect of consolidating research findings into clinical practice. The article also summarizes numerous openly accessible databases for researchers, enabling them to conduct deeper data mining and analysis using existing data. However, achieving such progress requires a more cautious selection of research models and techniques to delve into the molecular mechanisms involved in the onset of SIC. Addressing the common challenges in omics, especially in discerning causal relationships and reactive changes within the disease context, will require more precise and in-depth research approaches. Through the comprehensive application of various omics technologies, we can anticipate the provision of

**Table 2**
General omics databases.

| Tool | Data types | Purpose |
|---|---|---|
| Genomics | | |
| GenBank Overview (nih.gov) | Publicly available collection of annotated DNA sequences | To perform gene annotation, search for modification and variation information, etc. |
| GENCODE – Home page (gencodegenes.org) | All *human* and *mouse* genes are included. | Obtaining the reference genome |
| Ensembl genome browser 110 | Genome annotations for dozens of species. | Provide genome information, including gene localization, structure, functional annotations, etc. |
| Transcriptomics | | |
| Home – GEO – NCBI (nih.gov) | Archive and freely distribute microarray, next-generation sequencing, and other forms of high-throughput functional genomics data | Conducting gene expression analysis to identify differentially expressed genes and potential therapeutic targets, among other purposes. |
| Single Cell Portal (broadinstitute.org) | Single-cell RNA sequencing (scRNA-seq) data from various biological samples. | Browsing, analyzing, and visualizing single-cell gene expression data. |
| ImmGen Databrowsers | Gene expression data related to the immune system | Obtaining gene expression profiles of immune cells to better understand the functionality and regulation of the immune system |
| ArrayExpress < BioStudies < EMBL-EBI | Storage of chips and high-throughput sequencing data | Archives of functional Genomics. |
| miRBase | Contains information about the location and sequence of mature miRNA sequences. | Identifying and annotating miRNAs discovered in experiments, understanding the roles and regulatory mechanisms of miRNAs in the biological system. |
| Proteomics | | |
| UniProt | Manually curated high-quality protein sequences and annotation information, and computationally annotated, unreviewed protein sequences | Provides comprehensive protein information, supporting research in the fields of biology, biomedicine, and bioinformatics. |
| PRIDE – Proteomics Identification Database (ebi.ac.uk) | Proteomics data based on mass spectrometry (MS), allowing for the visualization of 2D gels and querying fractions. | Specialized in storing and sharing mass spectrometry data, including mass spectrometry identification and quantitative data. |
| RCSB PDB: Homepage | contains > 1 TB of Structure Data for Proteins, DNA, and RNA | Contains experimentally determined three-dimensional structures of biological macromolecules, primarily proteins. |
| The Human Protein Atlas | Proteome analysis based on 27,520 antibodies targeting, 17,288 unique proteins | Focuses on *human* protein expression and localization. |
| Metabolomics | | |
| Human Metabolome Database (hmdb.ca) | contains 220,945 metabolite entries including both water-soluble and lipid soluble metabolites | Provides extensive information about metabolites under physiological and pathological conditions, supporting metabolomics research and biomedical studies. |
| KEGG: Kyoto Encyclopedia of Genes and Genomes | A highly comprehensive and extensively utilized database that encompasses metabolic pathways. | Emphasizes the systematic nature of metabolic pathways, aiding in the understanding of the |

(*continued on next page*)

**Table 2** (*continued*)

| Tool | Data types | Purpose |
|---|---|---|
| | | metabolic network within living organisms. |
| metlin.scripps.edu/landing_page.php?pgcontent = mainPage | Includes mass spectrometry data, covering mass spectra of metabolites from various biological samples. | Focuses on mass spectrometry metabolomics, supporting the identification and quantitative analysis of metabolites. |
| MassBank \| MassBank Europe Mass Spectral DataBase | Various high-resolution mass spectrometry data. | Specializes in the storage and sharing of mass spectrometry data. |

more targeted and effective personalized strategies for the treatment of SIC.

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## CRediT authorship contribution statement

**Zheng Han:** Writing – original draft. **Zhen Quan:** Writing – review & editing. **Siyao Zeng:** Writing – review & editing. **Lianghe Wen:** Writing – review & editing. **Hongliang Wang:** Supervision, Funding acquisition.

## 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.

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