Research Advances in Biomarker for Sepsis

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Abstract Sepsis is one of the most common causes of death in severely injured patients worldwide. The early detection of sepsis still has to be solved in clinical practice. The delayed diagnosis often contributes to inappropriate antimicrobial treatment and subsequent high mortality. Sepsis biomarkers are produced during the host response to infection. Traditional biomarkers are polypeptides and/or proteins derived from this response. Omics-based biomarkers are screening out from all kinds of molecules of host response while high-throughout omics technologies are emerging. This review describes traditional and potential omics-based sepsis biomarkers from currently available literatures. The combination of these biomarkers would refine the identification of sepsis for further clinical and experimental sepsis studies.

Keywords Trauma · Sepsis · Diagnosis · Biomarker · Omics technology

1 Introduction

Sepsis is one of the leading fatal causes of critical injured and ill patients all over the world. Despite recent advances in comprehensive management of trauma patients, sepsis is still a life-threatening condition with poor outcome. The risk factors of patients for the development of sepsis usually refer to their physiological characteristics, underlying illnesses and clinical treatment backgrounds. The patients with one or more of these factors are susceptible to sepsis. The most vulnerable populations for sepsis are the elderly and infants, patients with chronic diseases, patients with severe trauma and burns, those who are immunocompromised or receiving immunosuppressive therapy, and malnourished and debilitated

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patients. Early diagnosis of sepsis plays a significant role for each hour of delay of appropriate antibiotic therapy increases mortality by 7.6 % [1]. However, the accurate and timely detection of sepsis remains a great challenge nowadays, because of the various, insidious and nonspecific clinical manifestations as well as the complex and indeterminate pathophysiologic process. Therefore, neither the clinical microbiological detection, which is known as the golden standard of infection, nor the most traditional biomarkers can fulfill all the existing needs in the early diagnosis and management of sepsis [2].

Originally, sepsis has been defined as infection with at least 2 of the 4 SIRS criteria, which mainly focus on inflammation that is not covered the full pathobiology. Sepsis is now recognized to involve early activation of both pro- and anti-inflammatory responses, along with major modifications in nonimmunologic pathways such as cardiovascular, neuronal, autonomic, hormonal, bioenergetic, metabolic, and coagulation, all of which have prognostic significance [3]. Sepsis is refined as "life-threatening organ dysfunction caused by a dysregulated host response to infection" [3]. There is an extensive and complicated pathogen-host interaction during the process of infection. Sepsis develops when the initial, appropriate host response to pathogens becomes amplified and then dysregulated [4]. It is the ability of host immunologic defense that determines the fate of infecting organisms: whether be localized, phagocytized and erased by immunocytes which may cause the release of their components from the invading pathogens; or multiply in the local tissues, successfully leak into the bloodstream and eventually become bacteremia and sepsis. Pathogen itself and its structural components not only cause extensive changes of both innate and acquired immunities, but also exert a profound influence on the systems of nerve, endocrine, respiration, circulation, and metabolism etc. [4]. Traditional biomarkers of sepsis are mainly derived from this host immuno-inflammatory response. The emergence and development of a variety of high throughput omics technologies will contribute to a more comprehensive screening for sepsis-specific biomarkers. Based on the discussion of current traditional sepsis biomarkers, we address new insights into sepsis biomarkers in the field of genomics, transcriptomics, proteomics, and metabolomics, those may show the hope for more comprehensive understanding of sepsis and help to overcome the present diagnostic uncertainty.

2   Traditional Biomarkers

Biomarkers are molecular indicators that help doctors diagnose illnesses, predict the outcome or identify which people are susceptible. Biomarkers, should be some quantifiable measurements of biological homeostasis and by defining the normal status can provide a frame of reference for predicting abnormal or pathogenic processes [2], and make an impact on clinical decision making in time. Most commonly proposed sepsis and infection biomarkers including C-reactive protein (CRP), procalcitonin (PCT) [5, 6], cytokines (TNF-α, IL-1, IL-6, IL-10, osteopontin) [7, 8],

chemokines [macrophage migration inhibitory factor (MIF), high-mobility-group box 1 (HMGB1)] [9, 10], soluble receptor [soluble triggering receptor expressed on myeloid cells 1 (sTREM-1), soluble urokinase-type plasminogen activator receptor (suPAR)] [11, 12] etc.

Given the complicated pathophysiology in sepsis which involves hundreds of mediators or single molecules, it is unlikely to identify one single biomarker which is able to satisfy all the existing needs and expectations in sepsis research and management. CRP, for example, is frequently used to assess the presence of infection and sepsis [2], and there is a positive correlation between its plasma level and the risk of organ dysfunction and death [13, 14]. However, plasma concentrations of CRP may increase during minor infection and do not adequately reflect the severity of infection, or remain at a high level for several days, even overstay the infection [2]. Besides, CRP may experience an increase during the inflammation caused by noninfectious etiologies, such as tumor, tissue necrosis or operation, which explains its nonspecificity as an early stage sepsis biomarker. Meanwhile, PCT, perceived as the most potential biomarker, is listed as one of the diagnostic criteria for sepsis [15]. A recent meta-analysis of PCT that included 30 studies found mean sensitivity and specificity of 0.77 and 0.79 respectively, with the area under the receiver operating characteristic curve (AUC) was 0.85 [16]. Although PCT was thought as a helpful biomarker for early diagnosis of sepsis in critically ill patients, it was not suitable to be recommended as the single definitive diagnostic test [16].

Therefore, some researchers have put forward that combinations of biomarkers may overcome the limitations mentioned above. In a prospective cohort study including 151 patients with systemic inflammatory response syndrome (SIRS), Kofoed et al. [17] found that the AUCs of six biomarkers—suPAR (0.5), sTREM-1 (0.61), MIF (0.63), PCT (0.72), neutrophil count (0.74), CRP (0.81)—for detection of a bacterial cause of inflammation had ranged from 0.5 to 0.81. With method reported by Xiong et al. [18], which discussed the statistical estimation of the optimum linear combination test and the associated maximum area under the ROC curve, Kofoed got the combined AUC of the six-marker test at 0.88. Consequently, the six-marker test had a better diagnostic accuracy in detecting bacterial versus nonbacterial causes of inflammation, and significantly greater than that of each single marker. Similarly, in another prospective research among the critically ill patients [19], a 'bioscore' combining the polymorphonuclear neutrophil (PMN) CD64 index together with PCT and sTREM-1 serum levels was put forward to diagnose sepsis and had a better performance with an AUC of 0.97 than that of each individual biomarker, and was externally confirmed in the validation cohort with 90.9 % of patients being correctly classified by the very model. Although the combination of biomarkers do improve diagnostic sensitivity and specificity, due to the factors of time-consuming, economic cost, the amount of sample, the feasibility of biomarker detection method and so on, it has a limited application in clinical practice and still needs further prospective studies conducted in multicenter on cost-effectiveness.

Circulating DNA, including nuclear DNA (nDNA) and mitochondrial DNA (mtDNA), can either actively release or be released passively into the blood stream after rupture or necrosis of host cells [20, 21]. These nucleic acids released in the plasma during sepsis could serve as danger associated molecular patterns (DAMPs) [22], which make them potential biomarkers for the very condition [23, 24]. A clinical study [22] found that plasma cytokine concentrations, as well as nDNA and mtDNA levels of septic shock patients were increased at the onset of septic shock and remained elevated. And during the first 5 days of septic shock, nDNA levels consistently correlated with plasma cytokine concentrations as well as with the shock-related parameter norepinephrine infusion rate and markers of organ damage (total bilirubin and creatinine). These findings not only indicate a relationship between plasma nDNA levels and the inflammatory response, but also demonstrate that nDNA levels are associated with markers of shock and organ damage in septic shock patients.

3 Genomics-Based Biomarkers

Genomics, a discipline in genetics and an emerging field, explains physiological or pathophysiological events from the point of view of complete set of DNA, including recombinant DNA, DNA sequencing methods, and bioinformatics to sequence, assemble, and analyze the function and structure of genomes. Sepsis can be regarded as a polygenic syndrome initiated by infection. Genetics plays a crucial role in both susceptibility and response to infection [25], and genetic predisposition influences clinical outcomes of infectious diseases [26, 27].

3.1 Polymorphisms and Single Nucleotide Polymorphism (SNP)

A gene polymorphism is defined as regular occurrence (>1 %) of two or more alleles at a particular chromosome location. Several polymorphisms of genes broadly involved in inflammation, immunity, and coagulation have been linked with susceptibility to sepsis, or outcome of sepsis [25], and have become the focus of most gene association studies of sepsis as well. SNP, the most common type of polymorphisms, is a substitution, deletion, or insertion of a single nucleotide occurring in approximately 1 per 1000 base pairs of human DNA. SNP can lead to an altered protein, a change in the amount of normal protein expression, or no discernible change in protein function [28]. Study of SNP genotypes in sepsis helps identify potential markers of susceptibility, severity, and clinical outcome.

Extensive researches on SNP genotyping of main genes CD14 [29–32], Toll like receptors (TLRs) [27, 33], lipopolysaccharide-binding protein (LBP) [34],

cytokines [26, 33, 35, 36] and coagulation factors [37, 38]—have provided valuable information for sepsis. For example, burn patients with TLR4 and TNF-α polymorphisms were 1.8 times more likely to develop severe sepsis, but none of them were significantly associated with mortality [33]. TLR1 SNPs are associated with increased mortality in patients with gram-positive sepsis after traumatic injury, which may represent a novel marker of risk for death in critically injured patients [27]. And most recently, it was found that there was a new association between vascular endothelial growth factor (VEGF) +936 CC genotype and the risk to develop acute kidney injury (AKI) in severe sepsis patients [35]. Genome-wide SNP genotyping assays allow to detect hundreds of thousands of SNPs accurately in a single experiment [39, 40] and are expected to be of great applicative prospect in finding novel sepsis susceptibility-associated SNP genotypes.

In order to evaluate the validity of these studies and translate this concept to the bedside, several important factors have to be kept in mind: potential confounding variables should be recognized and matched; positive association studies and replicate studies should be validated and analyzed on the basis of the primary hypothesis other than multiple comparisons; large scale collaborations and studies on sepsis susceptibility-associated SNP genotypes need to be performed for the sake of possible new risk factors at the genetic backgrounds of sepsis development [25, 41].

3.2 Epigenetics-Based Biomarkers

Genes concerning immunity and inflammation are subject to epigenetic regulation [25], which refers to heritable changes in gene expression that are not related to direct DNA sequence changes [42]. DNA methylation and histone post-translational modifications play vital roles in the epigenetic control [43] and gene expression, and strongly impact on the host defense responses.

Sepsis induces epigenetic changes in dendritic cells and lymphocytes rendering the host immune deficiency for a long period after the initial sepsis challenge [44–46]. Late-phase immunosuppression of sepsis is strengthened by a postmortem study [47]. By suppression of proinflammatory gene products and subsequent immune cell activation and proliferation, epigenetic mechanisms are put forward to have an influence on the very stage of sepsis, which may not only provide a better understanding of septic mechanism but also yield important biomarkers [48].

DNA methylation, the addition of methyl group to cytosine or adenine nucleotide, is now replacing the biological markers with their high specificity, sensitivity and prognostic efficacy. A retrospective investigation has showed that calcitonin-related polypeptide α (CALCA) gene promoter methylation varied with different types of preterm bacterial sepsis [49]. Based on this finding, another study demonstrated that global DNA methylation varied significantly among newborns with sepsis and those without sepsis [50]. More specifically, a recent study analyzed the CpG methylation status in the epigenome of septic and non-septic babies [51] or

ICU patients [52]. Given biological and clinical significance, they found 81 differentially methylated CpGs located in 64 genes, and a panel of differentially methylated protocadherin β (PCDHB) genes that play vital role in leukocyte cell adhesion and Wnt signaling pathway. These genes play vital role in calcium dependent cell to cell adhesion and other immunological processes like antigen processing and presentation. In sepsis, suppression of leukocyte cell adhesion and migration may exaggerate disease severity and poor outcome due to multiple organ dysfunctions. Therefore, this study provides some novel insights into the role of DNA methylation in neonatal sepsis. However, further studies are called for exploring the clinical relevance as well as related therapeutic approaches of the observed findings.

All the above mentioned sepsis biomarkers are derived from the development of genomics technology and summarized in Table 1.

Table 1 Potential genomic biomarkers for sepsis

Genomics	Biomarkers (reference)	Patients/animals (reference)	Changes	Clinical relevance (reference)
SNP	TLR1 [28]	1961 trauma patients	−7202G +742A/G (Asn248Ser)	Association with increased mortality after traumatic injury and sepsis
	CD14 [30–33]	14 septic patients and 30 healthy controls [30] 514 critically ill patients [31] 58 severely injured blunt trauma patients [32] 228 burn patients [33]	−260C → T	1. No association with an increased risk of severe sepsis in trauma patients [30] [32] 2. Association with increased susceptibility to sepsis [33] 3. Higher −260TT genotype frequency in ICU survivor patients [31]
	IL-6、TLR4 and TNF-α [33]	228 burn patients	IL-6 -174 G → C TLR4 +896A → G TNF-α -308G → A	Association with increased risk for severe sepsis after burn injury
CpG	81 differentially methylated CpGs located in 64 genes [51]	3 septic and 3 non-septic babies	Protocadherin beta genes (PCDHB11/12/16/5/6/7/9) hypermethylated in newborns with sepsis. CCS-hypermethylated, DEGS2-hypomethylated	Provide some novel insights into the role of DNA methylation in neonatal sepsis

4   Transcriptomics-Based Biomarkers

4.1   Gene Expression

The immune responses involved in sepsis are so complicated that the exact molecular mechanism remains to be fully elucidated [53]. The balance between pro-inflammatory responses and anti-inflammatory responses is closely related to the expression and regulation of relevant genes [54]. Hence, evaluating the key gene expression profiles by high throughput DNA chip may reveal the immune status of septic patients. Researchers have found specific changes of gene expression with microarray in certain organs and tissues of septic mice model, which including heart [55], liver, spleen [56], leucocytes [57] and so on.

Accordingly, Lukaszewsk recruited 92 ICU patients who had the risk of developing into sepsis [58]. The mRNA expression levels of IL-1β, IL-6, IL-8, IL-10, TNF-a, FasL and CCL2 in their blood leukocytes were measured on a daily basis by means of real-time reverse transcription PCR (RT-PCR), and analyzed with a nonlinear technique (neural network analysis). The data correctly predict the onset of sepsis in an average of 83.09 % of patient cases between 1 and 4 days before clinical diagnosis with high sensitivity and selectivity (91.43 and 80.20 %, respectively). Sutherland et al. [59] evaluated transcriptional profiles in circulating white blood cells of ICU sepsis patients, post-surgical patients and healthy controls with a microarray and multiplex tandem (MT)-PCR. A panel of 42-gene expression markers was identified, by which the prediction of sepsis within a mixed inflammatory population had an AUC between 86 and 92 %. Sepsis has a unique gene expression profile that is different from uninfected inflammation and becomes apparent prior to the clinical manifestations of sepsis for 0–48 h [60]. In that case, the specific gene expression profile, which may involve the function of innate immunity, cytokine receptors, T cell differentiation as well as the protein synthesis, may make a reference for early diagnosis of sepsis.

However, an important limitation of transcriptomics is that it only partially reflects the steady-state mRNA abundance, and the degree of mRNA abundance is influenced by multiple factors, and does not provide any direct information about gene end products (proteins), nor post-translational modifiers of protein function [61]. When it comes to the sample used as RNA source, there is a contradiction. For the whole blood approach, it may be difficult to interpret the confounded data of RNA for the reason of the heterogeneity among blood cell populations. As for the cell-specific approach, there is a possibility to miss relevant expression information from other cells due to the complexity of clinical sepsis [61]. It highlights the necessity of linking theory to clinical practice.

4.2   *miRNAs*

MicroRNAs (miRNAs) is a class of short RNAs with 18–25 nucleotides in length which regulate gene expression in a post-transcriptional manner via sequence-specific interaction with target sites in mRNA [62], associated with various physiological and pathological processes. The levels of miRNA in serum and plasma are consistent among individuals of the same species, resistant to RNase A digestion, and stable even after the freeze-and-thaw and a long term of storage [63, 64]. The stability of miRNA makes it a potentially useful candidate for diagnostic and other clinical applications. Although the source of circulating miRNA is still unclear, it has been proved that there is a link among a range of diseases, such as circulating miRNA and cancer [65, 66], trauma [67, 68], acute pancreatitis [69], and hepatitis [70].

When it comes to sepsis, by using genome-wide miRNA profiling with microarray in peripheral blood leukocytes and quantitative RT-PCR, Vasilescu [71] found that miR-150 levels were significantly reduced in both leukocytes and plasma of sepsis patients and had a negative correlation with the level of disease severity measured by the Sequential Organ Failure Assessment (SOFA) score, which made it a biomarker of early sepsis. Similarly, Zeng [72, 73] investigated the levels of miR-150 and miR-143 in peripheral blood leukocytes in sepsis patients with RT-PCR, and found that the expression levels of miR-150 and miR-143 were significantly decreased in sepsis patients and could reflect the severity of sepsis in certain degree, which not only made it a marker to reflect the situation of inflammatory response, but also made it a prognostic marker in sepsis. Recently, higher serum miR-133a levels were found among sepsis patients in ICU [74]. As they were significantly correlated with disease severity, classical markers of inflammation and bacterial infection, as well as organ failure, high miR-133a levels were considered as independent biomarkers for unfavorable prognosis of critically ill patients.

However, given that the pathophysiological process of sepsis involves a variety of tissues and organs, a simple screen for miRNA differentially expressed in leukocytes may omit those secreted by other cells. Wang et al. [75] used genome-wide microarray to identify differential serum miRNAs in survival and non-survival sepsis patients, and then further validated the differential expressions of miR-297 and miR-574-5p by RT-PCR in a larger group. The serum miR-574-5p together with sepsis stage and Sepsis-Related Organ Failure Assessment scores has a better predictive capability for the death of sepsis patients. In addition, serum miR-146a and miR-223 were found significantly reduced in septic patients compared with SIRS patients and healthy controls which might serve as new biomarkers for sepsis with high specificity and sensitivity [76]. Due to our knowledge on serum miRNAs is still at a primary stage, the expression level of circulating miRNAs at different stages of sepsis and their potential correlation with injured organs need further investigation.

To sum up, from the point of view of gene transcription, miRNA may undertake the task of diagnosing sepsis in an early stage and evaluating the prognosis, as well as becoming the new target for sepsis therapy.

4.3 Long Non-coding RNAs (LncRNAs)

As discussed above, epigenetic factors not only include histone modifications and DNA methylation, but also contain non-coding RNAs(ncRNAs), which have diverse size and can be generated from intergenic regions, introns, or enhancers [45]. LncRNAs are transcripts longer than 200 nucleotides and lack protein-coding capacity. Peng et al. [77] first discovered the widespread differential expression of lncRNAs in response to severe acute respiratory syndrome coronavirus (SARS-CoV) virus infection. Accordingly, there is a possible link between lncRNAs and the host defense response against infection. LncRNA has the potential to become new class of biomarkers and new therapeutic target for infectious diseases. However, as the functions of lncRNAs remain largely unexplored, there is a need for future studies on their regulatory role in infection.

All the transcriptomics-based biomarkers mentioned above are outlined in Table 2.

5 Proteomics-Based Biomarkers

Proteome is the complete set of proteins that can be expressed by the genetic material of an organism. Proteomics is the analysis of the expression, localizations, functions, and interactions of proteomes. Compared to other immunologic tests, proteomics is a novel method with advantages of high throughput, high sensitivity and specificity. The development of proteomics has allowed for a better understanding of the molecular bases concerning the identification of cell signaling, modifying protein, post-translation modification pathway, as well as the characterization of specific biological markers [78].

Proteomics has irreplaceable clinical significance and an expansive application prospect in studies of sepsis biomarkers. In a rabbit sepsis model by intravenous injection of *Pseudomonas aeruginosa* at 24 h after scald, 11 discrepant expression proteins from lymphocyte were found by matrix-assisted laser desorption/ionization time of flight mass spectrometry(MALDI-TOF MS). They are related with the folding, assembling, transportation and degradation of proteins, signal transmission, inflammation, immunization, energy metabolism, the proliferation, differentiation and apoptosis of cells [79]. In a recent research, 41 differential expressed proteins in the neutrophils from *Acinetobacter baumannii* sepsis rats were identified using two-dimensional electrophoresis and mass spectrometry [80]. They included antioxidant proteins, signaling proteins, cytoskeleton and regulatory proteins,

Table 2 Potential transcriptomic biomarkers for sepsis

Transcriptomic	Biomarkers (reference)	Patients/animals (reference)	Changes	Clinical relevance (reference)
Gene expression	A panel of 42 sepsis gene expression markers [60]	Mixed inflammation group (28 sepsis and 38 post-surgical patients in ICU), and 20 healthy controls	NA	A novel molecular biomarker test has the capacity for early detection of sepsis via the monitoring of patients
	IL-1β, IL-6, IL-8, IL-10, TNF-a, FasL and CCL2 mRNA expression [59]	92 ICU patients	NA	Provide a generic indicator of sepsis and help its early diagnosis
miRNAs	miR-150 [71, 72]	17 sepsis patients and 32 healthy controls [72] 40 sepsis patients,20 SIRS patients, and 20 health controls [73]	↓	The miR-150 levels in both leukocytes and plasma correlate with the aggressiveness and prognosis of sepsis and can be used as a marker of early diagnosis
	miR-133a [74]	223 critically ill patients(138 with sepsis and 85 without sepsis) and 76 healthy controls	↑	High miR-133a levels were associated with the severity of disease and predicted an unfavorable outcome of critically ill patients
	miR-143 [73]	40 sepsis patients, 20 SIRS patients and 20 healthy controls	↓	The expression level of miR-143 may be a marker for judging the severity of sepsis and its prognosis
	miR-146a [76]; miR-223 [76]	50 sepsis patients, 30 SIRS patients and 20 healthy controls	↓ ↓	Serum microRNAs might be used as biomarkers for early diagnosis and reflecting severity of sepsis
	miR-574-5p [75]	12 surviving and 12 nonsurviving sepsis patients for	↓	The miR-574-5p combined with SOFA scores and

(continued)

Table 2 (continued)

Transcriptomic	Biomarkers (reference)	Patients/animals (reference)	Changes	Clinical relevance (reference)
		microarray scan; 118 sepsis patients for validated by qRT-PCR		sepsis stage provides a prognostic predictor of sepsis patients

NA Not available

energy metabolism and protease protein, which may play a key role in such kind of sepsis and provide potential clues in early diagnosis and treatment of sepsis.

In clinic, YKL-40 was identified with proteomics analysis on a significantly higher expression level in serum samples from sepsis patients and considered as a possible biomarker of sepsis [81]. Paugam-Burtz et al. [82] used plasma profiling coupling proteinchip array with surface-enhanced laser desorption ionization time-of-fly mass spectrometry (SELDI-TOF MS) to analyze the plasma of post-operative patients, and found that a combination of five plasma protein peaks may have potential as diagnostic biomarkers of postoperative sepsis in patients undergoing liver transplantation. Even so, these proteins remain to be identified and validated in more clinical trials.

6 Metabolomics-Based Biomarkers

Although many potential sepsis biomarkers have been revealed by genomics, transcriptomics, and proteomics, the changes of cellular metabolism in sepsis should be paid attention. Metabolomics is an emerging omics technology following genomics and proteomics and focuses on the metabolic products with a molecular weight less than 1000 kD under the physiological or pathological status. It can analyze the biochemical events of cells, tissues or organs and evaluate the disease and its severity. The research methods of metabolomics mainly include nuclear magnetic resonance (NMR), gas chromatography/mass spectra (GC/MS), high performance liquid chromatography/mass spectra (HPLC/MS).

The development of sepsis involves the reactions of multiple systems on various levels, which has a significant influence on the expression levels and activities of metabolic enzymes. And by detecting the concentration and ratio changes of those metabolites involved, a better understanding of condition and prognosis of sepsis may be achieved at an early stage [83]. Metabolic profile of the serum from septic rats with cecal ligation and puncture was achieved with the help of NMR and LC/MS [83]. In the septic rats, especially the non-survivors, many free fatty acids

showed a lower level which may be consumed greatly for energy supply in sepsis and may be related with the prognosis of sepsis. Moreover, there was a rise of some polyunsaturated fatty acids in the very group, which may have a relationship with the increased anti-inflammatory effect. Based on the metabolic profile analysis, a model for outcome predication was built with high sensitivity and specificity, which provided a novel method for sepsis prognosis judgment. NMR-based metabolic profiling revealed the difference of metabolites of energy metabolism and inflammation in lung tissue, bronchoalveolar lavage (BAL) fluid, and serum samples between the septic rat and the control rat [84]. In septic rats, creatine concentration increased in all the three types of samples, whereas alanine and phosphoethanolamine concentrations increased only both in lung tissue and in serum. Myoinositol increased in lung tissue but decreased in BAL fluid. In addition, acetoacetate increased whereas formate decreased in serum. And with the construction of a predictive model for diagnosis of sepsis using partial least-squares discriminant analysis, the preliminary goal of sepsis diagnosis was achieved.

The possible sepsis biomarkers screened out from the application of proteomics and metabolomics technologies are summarized in Table 3.

Table 3 Potential proteomic and metabolomic biomarkers for sepsis

	Biomarkers (reference)	Clinical relevance (reference)	Changes	Patients/animals (reference)
Proteomic	YKL-40 [82]	YKL-40 may involve in the pathophysiology of sepsis and be a biomarker of sepsis	↑	45 sepsis or septic shock patients, 22 healthy controls and 23 patients who received off-pump coronary artery bypass grafting
Metabolomic	Acetoacetate, Alanine, Creatine, Phosphoethanolamine, formate [84]	NMR metabolomics analysis is a potentially useful technique for sepsis diagnosis	↑ (serum) ↑ (serum) ↑ (serum) ↑ (serum) ↓ (serum)	14 rats underwent cecal ligation and puncture as septic group;14 rats with sham procedure as control group
	Linoleic acid, Oleic acid, Atearic acid, Docosahexaenoic acid, Docosapentaenoic acid Linolenic acid [83]	A model for outcome predication was built with high sensitivity and specificity	↓ (serum) ↓ (serum) ↓ (serum) ↑ (serum) ↑ (serum) ↑ (serum)	23 surviving and 22 nonsurviving septic rats; 25 sham-operated rats

7 Prospects

Sepsis involves sophisticated pathophysiologic changes among various organs and different systems, so that comprehensively identifying sepsis biomarkers and understanding sepsis molecular mechanism from the perspectives of omics may provide valuable information about a more macroscopical and authentic state following infection.

The most important issue involved in the researches of sepsis biomarkers is the criteria of septic cases. The golden standard of infection, currently, still depends on the results of clinical microbiology laboratory, which, however, due to the severity of the disease, the load and type or growth capacity of pathogens, and the use of antibiotic treatment may show a negative result while patients has clinical manifestation of infection [85]. Or false positive results may present for the reason of contamination. Therefore, whether this gold standard is appropriate in sepsis needs further reflection and investigation.

There is a lack of effective and united assessment methods for sepsis biomarkers, especially in the multi-centered or multi-index researches. Valid evaluation needs to be performed to pick out the ideal diagnostic indicators, those both of high sensitivity and specificity in the field of data statistics and of great practical use in clinical practice.

Majority studies of sepsis only focus on a single set of omics technology (Table 1) rather than apply the combination of multiple omics approaches. Since different omics may display sepsis mechanism at various levels of a specific molecule or a particular group of sepsis-associated molecules, the comprehensive application of two or more omics may provide integrated information of potential sepsis biomarkers. MAPIT algorithm (Multi Analyte Pathway Inference Tool), for example, enables principled integration of epigenomics, transcriptomics, and proteomics data for cancer diagnosis, prognosis, and biomarker discovery [86].

Last but not the least, as mentioned above, the lack of a clear insight of the pathophysiology of sepsis process will, to some extent, put off the sepsis biomarker researches [2]. But with the application of state-of-art technology and exploration in a novel view, the progress in sepsis biomarkers will promote awareness and understanding of sepsis.

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