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An Overview of Proteomics on Sepsis

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Abstract

Over the last years, proteomics has provided us a lot of information about the spectrum of all the proteins that are expressed by an organism in pathological and non-pathological processes. The advantage of studying the proteome over other omics (genomics, epigenetics, transcriptomics and metabolomics) is that proteins reflect the final effectors in all the complex network of replication, transcription and translation.

Sepsis is a systemic inflammatory response caused by infection and that could produce multiple organ dysfunctions. The study of the secreted proteins would improve the knowledge of molecular mechanisms and pathways implicated in the septic process and consequently, data will allow us to find new therapeutic targets.

The objective of this review is to summarize the proteomics updates of preclinical and clinical studies of sepsis in fields like pathophysiology, treatment, diagnosis or prognosis, providing new perspectives and directions of sepsis.

Proteomics is a useful technique for the understanding of the pathophysiology of sepsis infection, the identification of new molecules for an early diagnosis and the prognosis, and the follow-up of treatment progress. The validation of new biomarkers needs a large cohort of patients and the use of other additional methods. Nevertheless, together with other techniques, proteomics has added important elements to the understanding of sepsis and other diseases. Despite current limitations, proteomic techniques improvement with bioinformatics tools might help results interpretation. Besides, the bettering in sensitivity and sensibility may facilitate further sepsis studies with these techniques.

Keywords: Proteome; Sepsis; Genomics; Epigenetics; Transcriptomics; Proteomics; Metabolomics

Introduction

Sepsis, a systemic inflammatory response caused by infection [1-3], together with multiple organ dysfunction (MODS), is a common cause of death in hospitalized patients worldwide. Sepsis is originated by multiple causes depending on the multiple injuring insults that may produce different clinical manifestations. Sepsis could be classified as "sepsis" when there is a systemic inflammation with a microbial process and "severe sepsis" if it is accompanied by an organ system dysfunction. The most serious process is called "septic shock" when hypotension is added to the anterior symptoms. Moreover, the sepsis process concomitant with dysfunction of two or more organ system is called MODS [3,4] (Figure 1).

The incidence of severe sepsis is 50-100 cases per 100000 people, and the mortality number surpasses 200000 cases per year in United States [5]. Sepsis affects patients of all ages. Neonates, elderly people and immuno compromised patients have more probabilities of developing sepsis. The aging population, the increase in high-risk surgical procedures and the development of infections increasingly resistant and virulent germs are the main causes of this disease. Recently it has been reported a declining in mortality rate in patients with severe sepsis and septic shock [6,7]. It has been proved that an increased severity correlates with an augmented mortality [8].

Over the last years, different tools as genomics, epigenetics, transcriptomics, proteomics, and metabolomics [9] have been used to investigate different fields of sepsis (Figure 2). Proteomic is referred to the application of high-throughput approaches to protein expression analysis. Nowadays, proteomic research is currently considered a 'hot topic' and is increasingly its application in human. Proteomics provides an analysis of the proteome, which is the spectrum of all the proteins that are expressed by an organism. Protein synthesis is the final result of gene expression (although not all mRNA expression leads to protein production) and is directly linked to the phenotype; this represents an advantage over other "omics". However, post-translational modification (processing from latent to active forms, glycosylation, phosphorylation and others) require further examination also. Usually the results of proteomics give us a list of all the expressed proteins in the different samples. Other specific proteomics methods allow evaluating the interacting proteins or specific pathway activation. Proteomics would improve the knowledge of molecular mechanisms and pathways implicated in the septic process and consequently, these data will allow us to find new therapeutic targets.

In the last years, proteomics has provided a lot of information and according to the precise role that proteins are involved; proteomics are classified in expression, structural and functional. Expression proteomics provides quantitative measures of proteins and compares the expression of the entire proteome or subproteomes between samples. Structural proteomics identifies all the proteins within a protein complex or organelle, determines where they are located and characterizes all the protein-protein interactions. Functional

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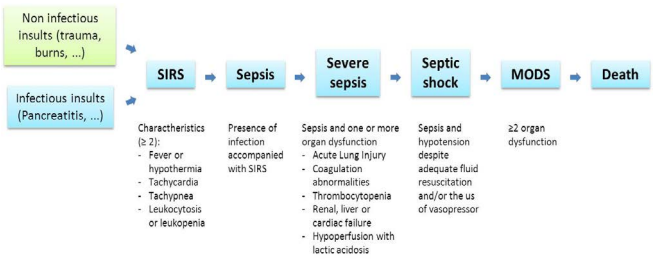

Figure 1: Infectious and non infectious insults can lead to systemic inflammatory response syndrome (SIRS). If SIRS is caused by infection, the term sepsis is used. When sepsis is accompanied by an organ system dysfunction progresses into severe sepsis and to septic shock when hypotension is added to the anterior symptoms. Multiple organ dysfunction syndrome (MODS) is defined as more than two organ dysfunction in critically ill patients. These circumstances can lead to death.

proteomics allows the study and characterization of a selected group of proteins, providing information about protein signalling, subcellular localization, post-translational modifications, disease mechanisms or protein-drug interactions, among others [10,11].

Different biological samples have been used in proteomics studies of sepsis, including fluids (e.g., plasma, serum, and urine), tissues (e.g., liver and heart), and cells (e.g., neutrophils, macrophages); each sample type, however, has advantages and limitations (4). To find some biomarkers low-abundance proteins must be detected. Some samples due to the technical difficulties associated with measuring the large dynamic range (~10–12 orders of magnitude) of proteins that exist in this medium need to be enriched. Enrichment strategies for low-abundance proteins rely on immunodepletion of high-abundance proteins or, more recently, tandem depletion strategies. These techniques are mostly applied to plasma or serum samples. There are various enrichment and depletion strategies such as shotgun proteomics techniques, liquid chromatography tandem mass spectrometry (LC-MS/MS) or capillary or two-dimensional protein electrophoresis (2DE).

After the correctly preparation of the sample, the protein detection and characterization must be performed. Mass spectrometry (MS) has a high specificity of protein detection and is a powerful analytical method. The mass spectrum of the protein will show any sequence variant, all the post-translational modifications or degradations.

MS demands specialized personnel and expensive instrumentation and now is starting to be used as routinely in clinical chemistry laboratories. MS is formed by an ionization source that could be MALDI (matrix-assisted-laser-desorption-ionization) or ESI (electrospray ionization) and a separating system that usually in proteomic techniques is TOF (time of flight).

An important distinction is made between full length protein analysis (top-down method) and peptide analysis after enzymatic digestion of the proteins (bottom-up method) and its implication for the protein assay. In the case of bottom-up methods before the MS analysis, an enzymatic digestion step of total protein is performed and only some peptides are detected.

Characteristics and possibilities of various top-down and bottom-up proteomic analytical programs are enormous.

A general workflow for proteomics analysis was described in this review (Figure 3), evidently, other approximations and modifications of it could be applied depending on the sample and the objective of the study. We describe the use of proteomics in sepsis and in this review, we summarize the proteomics updates of preclinical and clinical studies of sepsis in fields like pathophysiology, treatment, diagnosis or prognosis, providing new perspectives and directions of sepsis.

Sepsis Pathophysiology

Over the last decade, advances on proteomics and other techniques have revealed many components of the pathogenesis of sepsis infection [4]. Sepsis pathophysiology is originated after the insertion of an external agent of infectious origin into an organism, producing a sequence of biological events in immune cells, epithelium, endothelium and the neuroendocrine system, and inducing a systemic inflammatory response syndrome (SIRS) [13]. Moreover, sepsis pathophysiology is determined by the relationships established between the etiological agent and the host [14,15].

The infectious agent activates the innate immune response system via the pattern recognition receptors (PRRs). PRRs recognize specific invariant structures of the microorganisms, called pathogen-associated molecular patterns (PAMPs), which are surface molecules such as the lipoteichoic acid of gram positive bacteria or lipopolisacaride (LPS) or endotoxin of gram negative bacteria. [13,16]. PRRs are cell structures encoded by the germinal cell lines and expressed by innate immune system cells [14]. One of the most known families of PRRs, the Toll-like receptors (TLRs) family, have been identified in the surface of monocytes, macrophages, dendritic cells and neutrophils [17].

Adaptor molecules that bind to the PRRs and protein kinase and phosphatases induce a signal transduction cascade, activating transcriptional factors like nuclear factor-kapaBeta (NF-kapabeta) [13], activator protein-1 (AP-1), CCAAT-enhancer-binding protein (C/EBP) family, Early Growth Response Protein 1 (EGFR-1), p53 or Signal Transducer and Activator of Transcription 1 (STAT1), and triggering the resulting SIRS. A complex network of inflammatory cytokines and anti-inflammatory cytokines is produced as a result of the receptor binding and the activation of signaling events [15].

In addition, host tissue damage expresses endogenous equivalents of PAMPs, called Damage-associated Molecular Patterns (DAMPs), like high mobility group protein B1 (HMGB-1) [18] or mithocondrial DNA [19], which are also recognized by PRRs [16]. Eukaryotic microorganisms, such as fungi, can either develop a sepsis [13].

Moreover, microorganisms stimulate specific cell-mediated adaptative immune responses; B lymphocytes release immunoglobulins that bind to pathogens, facilitating their recognition by natural killer cells or neutrophils [20] and activate the adaptative immune system [21]. T-helper 1 (Th1) lymphocytes are stimulated by the phagocytosis of bacteria or necrotic cells by macrophages, segregating pro-inflamamatory substances. T-helper 2 (Th2) lymphocytes are activated for example when macrophages phagocytize apoptotic cells, releasing anti-inflammatory particles [15,20].

Furthermore, another important aspect of sepsis is the disturbance of the pro/anti-coagulant balance, as the fibrinogen deliverance is up-regulated and antithrombin liberation is repressed [14,20].

The complex altered signaling networks in sepsis, produced by the activation of the innate and acquired systems and the deregulation of inflammatory and coagulant factors, might ultimately lead to tissue injury and multiorgan dysfunction [20,22]. Nowadays, it is a challenge to obtain new specific biomarkers because of the host response heterogeneity.

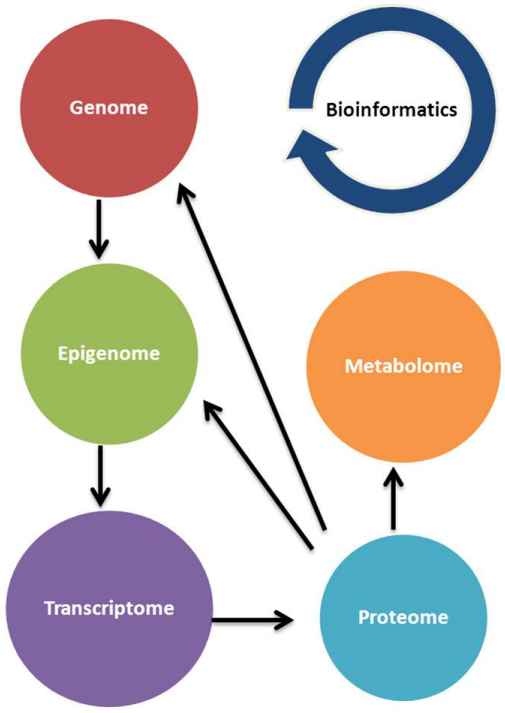

Figure 2: Schema of "omics" sciences that could contribute to biological studies. Proteomics is referred to the application of high-throughput approaches to protein expression analysis. Proteins could modify the genome, epigenome, transcriptome and metabolome expression.

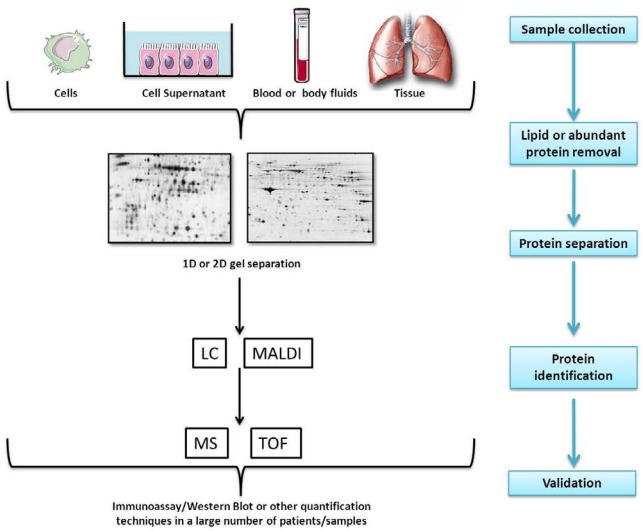

Figure 3: Workflow for proteomics analysis. LC (Liquid Chromatography), MALDI (matrix assisted laser desorption ionization), MS (mass spectrometry) and TOF (time of flight).

Our knowledge about the complex network of the pathophysiology has increased thanks to proteomics. In a recent study, Dalli et al. [23] investigated the proteome of neutrophil microparticles in patients and demonstrated that in a directed stimulation neutrophil microparticles produced reactive oxygen species, leukotriene B4 and a chemotactic gradient. Moreover, granzymes proteases have been evaluated by proteomics to understand the physiological role of these proteases in sepsis, although it is presently unclear which granzymes are physiologically relevant [24]. Furthermore, changes on platelet function in rats with sepsis were analyzed by proteomics, providing platelet profiles and new insights on the understanding of platelet dysfunction in sepsis [25]. Additionally, Paiva et al. [26] employed proteomic techniques on serum samples collected from each stage of sepsis to study the molecular foundations of sepsis, demonstrating the involvement of complement and coagulation pathways, of lipid metabolism and of genetic information in sepsis.

Sepsis Diagnosis and Prognosis

A great number of biological substances have been investigated as mediators and biomarkers for sepsis diagnosis. Some markers give us information about the severity of sepsis, although part of them with huge limitations. Proteomic approach is usually employed to identify proteins that are upregulated or downregulated in sepsis-specific manner for use as diagnostic and prognosis markers. In the last recent years there were identified a varied range of compounds that are useful as biomarkers for this pathology [4,27].

The use of biomarkers together with the prognosis scores allows us to predict the beginning of sepsis process and the outcome of this sepsis, evaluating the different stages of sepsis. In the prognosis evaluation of sepsis are usually used different scores such as APACHE II and SOFA [28,29]. All these scores evaluate the six organ systems (respiratory, renal, hepatic, cardiovascular, hematological, and neurological) and rank their risk of dysfunction. The MODS are one of the worse prognostic markers and all the clinical scores are targeted to evaluate it.

Protein profiles of patients in different sepsis stages present variances, suggesting that the progress of the disease could be predicted evaluating some specific proteins. Proteomic techniques offer the opportunity to detect specific proteins in preliminary stages of sepsis and allow physicians to start selected treatments in a preventive way such as an appropriate antibiotic therapy. As it is known, the treatments administered early have a beneficial effect in the survival of patients [15].

The early sepsis diagnosis only using clinical elements and prognosis scores is difficult and the addition of other factors that can delineate better the disease will be useful. The evaluation of the inflammatory status of the patients in a preliminary point will give to the clinicians the tools to modify the therapeutical approximations that this patient need.

For diagnostic there are different biomarkers that showed increases in septic patients. In the last years, few studies using proteomics and sepsis prognosis have been published too [30].

C-reactive protein, a calcium dependent binding plasma protein (CRP) is increased in the acute inflammatory response phase and is one of the most used markers of infection in critically ill patients [31]. Moreover it is used as a prognostic biomarker too, because CRP is able to predict prognosis and severity [32]. CRP usually is measured daily in the critical care units as a tool to predict outcome and to evaluate the effect of the antibiotic; patients that showed a decreased in CRP daily have better surviving taxes [32,33]. Another useful biomarker is procalcitonin (PCT) [34], a prohormone of the hormone calcitonin which is produced in neuroendocrine C-cells. When there is an infection, there is an increase of PCT production. In these conditions PCT is released in all tissues such as liver, adipose tissue, kidney, and muscle [35]. PCT could be a valuable diagnosis biomarker because it

has a peak between 8 and 24 hours after the infection PCT increases with the severity of sepsis and organ dysfunction, and for this reason clinicians evaluated the use of PCT as a prognosis biomarker [35,36]. Diverse studies conclude that PCT failed to predict prognosis and other scores such as SOFA had better prediction of mortality than PCT. IL-6 is considered useful in the diagnosis of sepsis however it is non-specific marker of systemic inflammation and its alteration could be produced by diverse factors. IL-6 levels correlate with mortality and organ failure, being a prognostic tool too. Three of them are used in sepsis, however, none of them are specifically for sepsis and none of them alone is a biomarker for sepsis. To find a new specific biomarker related to sepsis and with diagnosis and prognosis value is one of the aims of research proteomic in sepsis.

Triggering receptor expressed on myeloid cells 1 (TREM-1) is a new family of receptors expressed on myeloid cells; in polymorphonuclear cells and monocytes in human and murine. TREM-1 expression rise when there is an infection such as during sepsis. Gibot et al. [37] found that plasma concentration of TREM-1 in infected patients performed better than concentrations of CRP and PCT [38]. Gibot et al. also evaluated TREM-1 as prognostic biomarker and they found that levels were higher and declined progressively in survivors, allowing discrimination between survivors and non-survivors [39]. Results are not confirmed in other studies.

YKL-40 is a novel biomarker detected by proteomics analyses in septic patients. YKL-40 is a glycoprotein secreted by macrophages, chondrocyte and others, involved in inflammation and tissue remodeling. In the study of Hattori et al. YKL-40 had a high expression in serum samples from septic patients and it was detected too in postoperative sepsis. Nevertheless, YKL-40 must be assessed in other clinical trials despite this first promising result, as it is necessary to validate its diagnostic value [40-42].

Paugam-Burtz et al. [42] identified five peptides that are useful as biomarkers to identify sepsis. In other studies the protein profile of septic patients were analyzed and showed 29 differentially expressed proteins compared with the non-septic group [43]. These different proteins are now being identified, because some of them have unknown function [44]. Afterward, these proteins have been validated for their use as biomarkers in diagnosis and prognosis of sepsis.

At the moment, researchers and clinicians are focused on combine different biomarkers because they know that an individual score or an individual biomarker have a lot of limitations. A lot of proteins are tested as diagnosis and prognosis biomarkers with good results, and their combination could improve sensitivity and specificity and prediction of disease.

Selberg et al. [45] compared PCT and complement 3a (C3a) in combination with PCT, IL-6, C3a, elastase, and CRP individually in identifying sepsis. Shapiro et al. [46] did a multicenter study with 971 patients for developing a sepsis score with a biomarker panel. Initially they analyzed 9 biomarkers but finally only 3 biomarkers were used to derive the score. The biomarkers that they chose were neutrophil gelatinase-associated lipocalcin, protein-C, and IL-1 receptor antagonist. Kofoed et al. [47] showed the ability of 4 composite biomarkers for the prediction of mortality. Dhainaut et al. [48] created a complex coagulopathy score that in combination with the APACHE II score, was able to predict 28-day mortality and organ failure better than APACHE II score alone.

Nowadays, researchers and clinicians try to correlate some scores as APACHE II and SOFA with pro-inflammatory and anti-inflammatory cytokines, as well as, PCT and CRP. This correlation or the combination of different biomarkers must be the strongest candidate to predict clinical outcome in patients with sepsis. It is really necessary the find of new biomarkers that would help in a better diagnosis and prognosis of sepsis.

Sepsis Treatment

Of course, proteomics is beneficial in preliminary diagnosis, prognosis and a better understanding of pathophysiology; however proteomics could be really useful in the sepsis treatment. The modulation of some cytokines, promoting or blocking them, could have interest in the disease treatment.

Techniques of continuous renal replacement therapy (CRRT) have been employed to treat septic patients in the critical care units [49]. The removal of some inflammatory mediators could be an important tool to bettering the septic process. The fluctuations in inflammatory markers in serum or plasma are not clear associated to CRRT and the beneficial effect is not clear [49,50].

Gong et al. [51] evaluated the proteome changes in patients with severe sepsis on CRRT and they found changes in abundance of 10 proteins; three were increased during CRRT and 7 were reduced in serum during CRRT. The proteins were: CD5 antigen-like precursor, syntaxin-b1B1, apolipoprotein A-IV precursor, apolipoprotein B-100 precursor, gamma-A isoform of fibrinogen gamma chain precursor, isoform 2 of ubiquitin E1-like activation enzyme, 36-kDa protein, MYH2 protein and SPTAN1.

In their study, Holly et al. identified changes in rat urinary proteins such as albumin, meprin-1-alpha and serine protease inhibitors [52]. Meprins have been implicated in the pathogenesis of several inflammatory diseases in which the cytokine interleukin-6 (IL-6) is an effector molecule; one function of meprin is to modulate inflammation by inactivating IL-6 [53]. Meprin inhibition prevents *in vitro* hypoxic injury and *in vivo* ischemia/reperfusion injury. In animal experiments the treatment with with meprin inhibitor prevented acute renal failures demonstrating the potential use of meprin as a sepsis biomarker and drug target in sepsis treatment.

Advantatges and Limitations of Proteomics

Proteomics analysis is a highly sensitive peptide screening that exposes protein expression, distribution and function. Compared with traditional protein biomarker technologies, proteomics have the advantage to analyze an unlimited number of proteins simultaneously, being less restrictive than ELISA and multiplex technologies [9], although proteins need a large amount of pre-processing or pre-fractioning. Additionally, there is no need of antibody-based technologies for the measure of proteins [9]. Unfortunately, proteomic techniques are inefficient in the quantification of low expression proteins, however new enrichment techniques are now available and allow us to detect them.

Furthermore, in contrast with genomics or transcriptomics, proteomics evaluates the biological pathways networks in response to disease that are expressed at the mRNA or protein levels, including details of all post-translational modifications and protein abundance, activity or location within a cell [9,12,15].

Proteomics is useful for the understanding of the pathogenesis of sepsis infection, the identification of new molecules for an early diagnosis and prognosis, and the follow-up of treatment progress. However, diagnosis and prognosis of sepsis provides challenges because

of the variability of clinical signs and symptoms [3]. Furthermore, these new biomarkers need to be validated by other techniques such as ELISA or Western Blot before their use in clinical practice [54].

Additionally, the employment of a small number of subjects to detect new biomarkers and the techniques employed that are too time-consuming makes that proteomics do not have statistical power because of it is necessary larger cohort samples and the use of additional methods to validate new biomarkers [4].

Nevertheless, together with other techniques, proteomics has added important elements to the understanding of pathophysiology, diagnostic, prognostic and treatment of sepsis and other diseases. Despite current limitations, the emergences of new, more economical and cost effective technologies are necessary before protein analysis on a large-scale becomes a reality.

The improving of other proteomic techniques, such as bioinformatics tools that help the results interpretation and the bettering in sensitivity and sensibility may facilitate further sepsis studies with these techniques.

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