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Review

From traditional biochemical signals to molecular markers for detection of sepsis after burn injuries

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ABSTRACT

Sepsis is a life-threatening organ-dysfunction condition caused by a dysregulated response to an infectious condition that can cause complications in patients with major trauma. Burns are one of the most destructive forms of trauma; despite the improvements in medical care, infections remain an important cause of burn injury-related mortality and morbidity, and complicated sepsis predisposes patients to diverse complications such as organ failure, lengthening of hospital stays, and increased costs. Accurate diagnosis and early treatment of sepsis may have a beneficial impact on clinical outcome of burn-injured patients. In this review, we offer a comprehensive description of the current and traditional markers used as indicative of sepsis in burned patients. However, although these are markers of the inflammatory post-burn response, they usually fail to predict sepsis in severely burned patients due to that they do not reflect the severity of the infection. Identification and measurement of biomarkers in early stages of infection is important in order to provide timely response and effective treatment of burned patients. Therefore, we compiled important experimental evidence, demonstrating novel biomarkers, including molecular markers such as genomic DNA variations, alterations of transcriptome profiling (mRNA, miRNAs, lncRNAs and circRNAs), epigenetic markers, and advances in proteomics and metabolomics. Finally, this review summarizes next-generation technologies for the identification of markers for detection of sepsis after burn injuries.

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Contents

1. Introduction

Following a severe burn injury, the body must respond immediately to activate the immune system in order to challenge the insult and to restore homeostasis while also preventing any bacteria from establishing an infection [1]. However, burns can leave skin and other tissues vulnerable to bacterial infection and increase the risk of sepsis (Fig. 1A). Sepsis is defined as life-threatening organ dysfunction [2–4] caused by a dysregulated host response to infection [5]. This process is regarded as a major public-health concern, with the mortality rate, depending on the severity of the insult, ranging from 30 to 50% [6]. A recent study demonstrated that mortality in patients with sepsis after burns was 34.4% [7], which can be increased due to the lack of adequate medical units and services for the treatment of this type of patient. According to some reports, the risk of mortality increases by ≈8% for every hour that adequate pharmacological therapy is delayed; thus, early diagnosis of sepsis is vital [8]. However, precisely timed detection of sepsis is a difficult challenge due to of its diverse, non-specific clinical signs and its incompletely understood pathophysiology. In addition, the diagnosis and therapy of sepsis is even more difficult in the burned patient, who is possibly at an even higher risk than the general critical-care patient. Today, the gold standard for identifying sepsis is the detection of a large panel of etiological agents; however, analysis of biochemical and microbiological cultures is impractical. Thus, it is necessary to identify new non-traditional biomarkers for the early diagnosis and treatment of sepsis [9]. In the last few years, a growing body of evidence has resulted in better understanding of the pathophysiology of burn injuries, but the whole process remains unknown at present and even more the process for sepsis development after burn injury.

In burn injuries, it is known that the destruction of the cutaneous barrier is followed by hypovolemic shock and a hypermetabolic response leading to an organic dysregulation that gives rise to greater susceptibility to infection (Fig. 1A) [10–12]. After a burn, several processes, such as hemostasis and inflammation, neovascularization, fibroplasia, contraction, retraction, and coagulation, are initiated. The initial stage involves heat-induced protein denaturation, inflammation, ischemia-induced injury, and cell death, which cause burns of diverse depth. At the molecular level, is evident the production of free radicals such as superoxide, hydroxyl, hydrogen peroxide, nitric oxide, nitroperoxide, alkylperoxyl, and lipid radicals [10]. The organism's pathophysiological response to burns is the release of proinflammatory substances that may lead to different clinical stages, according to the body-surface area injured. The main risk after burn injury is a subsequent infection, however the colonization rate depends on multiple variables, such as the mechanism of the injury, the size and depth of the burn, the environment, translocation of pathogenic bacteria and whether timely first aid was offered [11]. Additionally, the anti-inflammatory response and subsequent immunosuppression resulting from burn injury are characterized by the production and release of cytokines and monocyte/macrophage

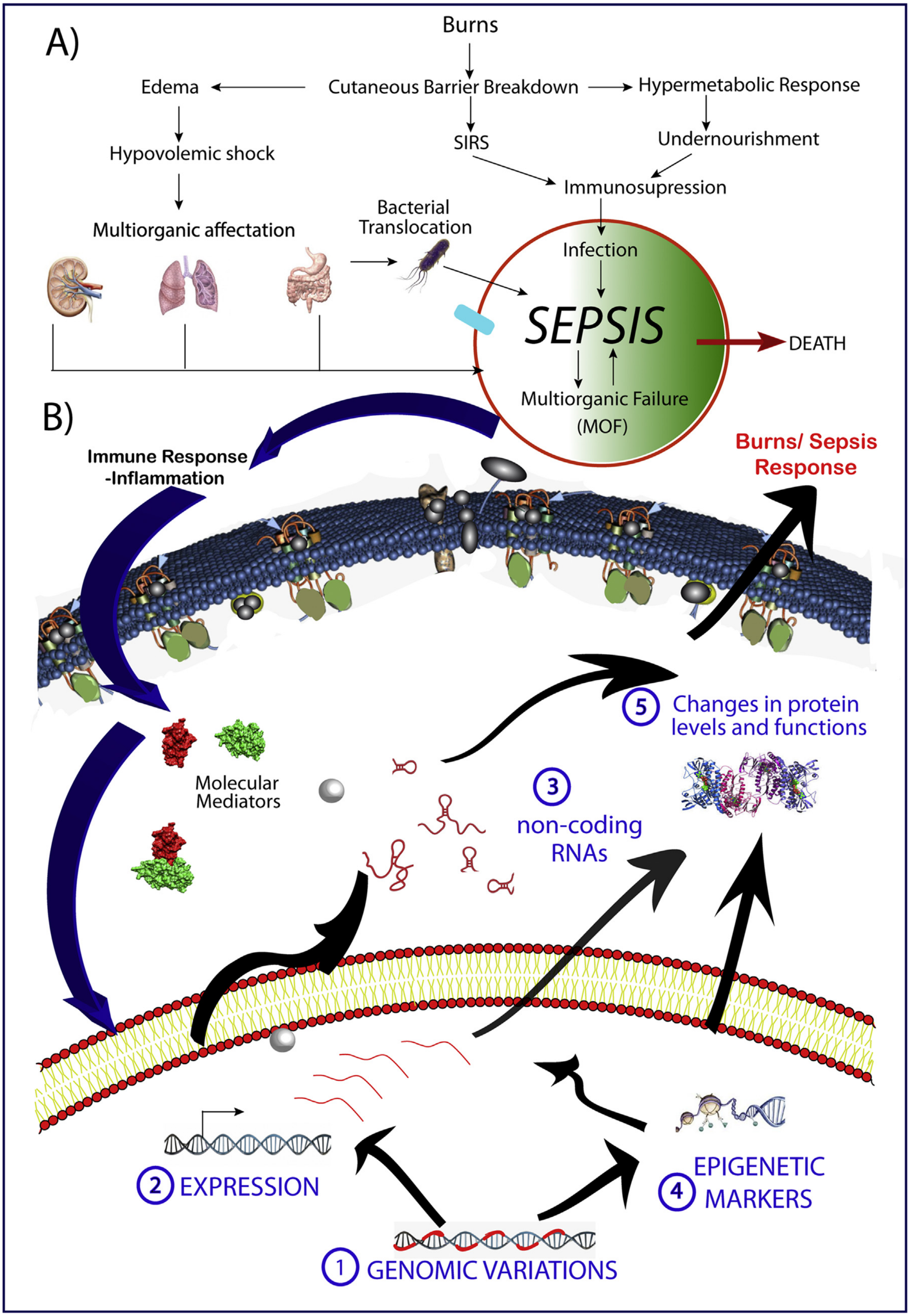

Fig. 1 – Systemic and molecular response to burn injury. (A) In response to severe burn injury, several complications could be presented, including edema, cutaneous barrier breakdown and hypermetabolic response, which in turn could eventually lead to sepsis. (B) Immunologic response provoked by sepsis is transduced into the cell by a variety of molecular mediators which

dysfunction, which also can result in many complications, such as septic shock, massive organ dysfunction, and even death (Fig. 1A) [11–13].

It is noteworthy that the idea of predicting complications of burned-related infections has been under discussion for 30 years [14]. Initial approaches were focused on understanding of the immune response [15,16], as well as on the characterization of pathogens isolated from various tissues of affected patients [17]. Novel knowledge about molecular and cellular mechanism involved in burn-associated sepsis, both in patients and in animal models, has contributed to the identification of sensitive and specific new biomarkers [18–22] for the development of sepsis. We present here a detailed review of novel markers that may contribute to early diagnosis of burn-wound infections and sepsis. We focus on diverse techniques based on genomic, transcriptomic, proteomic, and metabolomic tools that could provide new insights into early potential indicators of sepsis after burn injury.

2. Current biomarkers in burn injury sepsis

Many protein markers have been suggested to date, including hormones, cytokines, chemokines, acute-phase proteins, soluble receptors, enzymes, and vascular markers, among others (Table 1). The presence of these proteins in serum or tissue as indicative of damage and sepsis progression represents the initial tool of diagnosis. However, these current biomarkers for sepsis are limited to supportive diagnosis and partially predict the outcome of illnesses. Traditional protein and enzymatic markers are predominantly derived from the host immune and inflammatory response; nonetheless, sepsis and post-trauma burn injury involves a variety of molecular complexes, mediators, and the activation of multiple signaling pathways, giving rise to that the use of a single biomarker or a limited number of these cannot satisfy all of the requirements for the diagnosis of sepsis. The current most common burn sepsis markers are described below.

2.1. Cytokines

The study of cytokines, such as Tumor Necrosis Factor alpha (TNF-α), basic Fibroblast Growth Factor (bFGF), and Interleukin-6 (IL-6), IL-8, or IL-10 as biomarkers of burn sepsis present in serum, has increased during recent years [23]. Many of these markers are highly related to the immune response triggered by infections and by the intensive damage associated to the burned tissue [24]. IL-6 mediates inflammatory responses, and during sepsis, the plasma levels of this cytokine are increased [25]. Higher levels of IL-6 in patients with sepsis were observed compared to non-septic and healthy subjects, suggesting that this cytokine may possess a role in the pathogenesis of sepsis in burned patients [26]. Furthermore, IL-6 with a cutoff of >500 pg/ml had sufficient discriminating power to differentiate between sepsis and non-infectious Systemic Inflammatory Response Syndrome (SIRS) [26]. In another study, there were significant differences in serum IL-6 values among patients who survived or died, or among patients with a total body-surface area of >50% or <50% from the burn injury [27].

In addition, IL-8 participates in the activation of neutrophils, tissue-repair mechanisms (such as cell proliferation and angiogenesis), and general inflammatory processes [28] whereby IL-8 may be pivotal for survival following burn injury. The levels of IL-8 in burn and septic patients rose significantly and the cutoff level for IL-8 as survival predictor was established as 234 pg/ml, [29]. Otherwise, the levels of IL-10, an anti-inflammatory regulatory cytokine, have demonstrated a positive correlation with the development of sepsis, and even more IL levels may discriminate between survivor and non-survivor septic patients [26]. Finally, TNF-α, a central regulator of inflammation, has been suggested as a relevant mediator of the inflammatory response in sepsis and septic shock. In burned patients, the levels of this cytokine were elevated in non-survivor with proven sepsis patients in contrast to patients who survived [30,31].

Despite being good markers, these levels may be biased by a variety of factors, such as multiple organ dysfunction, post-burn assessment time, and multiple confounding variables and comorbidities, as well as by interindividual genetic variability. Therefore, it is necessary to have a suitable battery of markers that confirm the septic state in the patient.

2.2. Procalcitonin, calcitonin, and the calcitonin gene-related peptide

In sepsis, systemic infection, and severe inflammation, the serum levels of Procalcitonin (PCT) [32,33] usually increase [34], so that this marker has been widely suggested in several studies as an indicator of infection [35,36]. Under normal conditions, all serum PCT is cleaved by a specific protease, producing calcitonin, catacalcin and an N-terminal residue; therefore, serum PCT levels are undetectable in healthy humans. Contrariwise, in severe infections, serum PCT levels may increase to >100 ng/ml. The performance of PCT as an early sepsis biomarker was superior to other usually available biomarkers, and a meta-analysis study revealed that PCT has a mean specificity of 0.79 and a mean sensitivity of 0.77 [37]. However, it is noteworthy that several variable characteristics of patients, such as burn size, surgical procedures, and analytic devices, among others, may influence PCT levels [35]. In addition, it has been shown that the Calcitonin Gene-Related Peptide (CGRP), a peptide produced by alternative RNA processing of the calcitonin gene, is released from nociceptive sensory endings in response to burn injury. CGRP contributes to the spread of edema by acting directly on venules producing vasodilation. Moreover, it affects the regulation of local blood flow, smooth muscle tone, and glandular secretion. In burned patients, baseline levels of CGRP were higher than in healthy controls, and the highest systemic CGRP levels from initial stages of sepsis were associated with lethal outcome [38].

together with 1) genomics variations, 2) changes in gene expression 3) non-coding RNAs, 4) epigenetic biomarkers, and 5) changes in protein levels and function, trigger the sepsis response. Among these, some specific molecular events have emerged as novel burn/sepsis biomarkers.

Table 1 – Diverse protein biomarkers in burn sepsis.

Type	Biomarker	Reference
Acute phase Proteins	Procalcitonin	[35,36]
	Pentraxin 3	[48]
	Serum amyloid A	[48]
	C-Reactive protein	[157]
	LPS Binding protein	[158]
Anticoagulant factors	Antithrombin	[168]
	Protein C	[169]
Chemokines	Motif Chemokine Ligand 8 (CXCL8)	[29]
	IP-10 (CXCL10)	[19]
Cytokines	Interleukin-6	[26]
	Interleukin-10	[26]
	Interleukin-13	[162]
	Interleukin-18	[162]
	Interleukin-27	[162]
	Tumor necrosis factor	[163]
Damage associated molecular patterns	DAMPs	[161]
Enzymes	Metalloproteinase	[58]
	Granzyme A	[55]
Growth factor	Thrombopoietin	[170]
Hormone	Leptin	[19]
	Testosterone/oestradiol	[156]
	Vasopressin/copeptin	[164]
	Natriuretic peptides	[165]
Receptors	TLR4	[86]
	Soluble TNF R	[31]
	Soluble CD14	[166]
	Soluble ST2	[167]
Surface glycoprotein	Thrombomodulin	[51]
Tissue injury biomarkers	Hyaluronan	[65]
	Pancreatic stone protein	[65]
	Lactate	[159]
	Heat shock proteins	[160]

2.3. C-reactive protein

The role of C-reactive protein (CRP) in acute inflammation is not completely understood. It may bind the phospholipid components of pathogens and damaged cells, promoting the removal mediated by macrophages. Since early stages of acute inflammation and infection, the levels of CRP increase much more significantly than the levels of other markers [39]; therefore, it may be used as adequate marker for immediate analysis addressed to detection of infection after burns. Nevertheless, it has been reported that CRP is incapable to reflect the severity and time course of the infection, because its level rises during mild infections and remains high through the infection's time course [40]. Some authors had proposed that combined detection of PCT and CRP may create a scoring system and improve early identification of infection in patients with sepsis with better sensitivity, however it is not yet possible to use it as severity markers [41].

3. Combination with potential new biochemical markers

The use of different combinations of the previously mentioned biomarkers could overcome their individual limitations [42–44]. However, diverse researchers have attempted to identify novel markers that provide greater reliability in the detection of early sepsis and that might be of relevance in the study of burn patients. Thus, we now describe possible markers that have demonstrated statistically significant differences in a process of sepsis in study models for burns and that could comprise an adequate complement to the markers currently used.

3.1. CD14

CD14 is the receptor of the Lipopolysaccharide (LPS)-Lipopolysaccharide Binding Protein (LBP) complex. Two forms have been identified: membrane-bound CD14 (mCD14), and soluble CD14 (sCD14). It has been shown that CD14 may activate inflammatory cascades and signal transduction pathways that lead to a systemic inflammatory response. In blood, sCD14 can be cleaved by proteases that generate a short form of 64 amino-acid residues known as sCD14-SubType (sCD14-ST), or presepsin. It is noteworthy that presepsin appears to possess better specificity and sensitivity in the diagnosis of sepsis that other biomarkers, such as PCT, CRP, and IL-6 [45]. A meta-analysis found that blood presepsin was an effective biomarker for the diagnosis of sepsis in a threshold ranging from 317 to 729pg/mL [46].

3.2. *Vasopressin*

Vasopressin is a powerful hormone that is responsible for regulating the volume and osmolality of plasma. It is bound to the carrier protein neurohypophysin, which participates in its transport along the supraoptic hypophyseal tract to axon terminals [47]. At initial phases of septic shock, the plasma vasopressin levels are increased, but it decreased afterward, in late septic patients. Hence, levels of vasopressin may be good candidates for evaluating the risk and prognosis of septic shock [48]. Further studies are necessary to prove their useful as early marker of sepsis.

3.3. *Thrombomodulin*

Thrombomodulin (TM) is a 557 amino-acid protein with several physiological roles. It is a protein cofactor expressed on endothelial cell surfaces that modifies the substrate specificity of thrombin. The thrombin–thrombomodulin complex inhibits fibrinolysis, activates protein C, and starts an essential anticoagulant pathway. After injury, TM is released from surfaces of endothelial cells by proteolytic degradation, producing soluble TM [49]. Increased serum TM levels have been documented in patients with septic shock compared to healthy controls [49]. It is noteworthy, that a higher TM level was observed in patients with severe sepsis, compared to patients with mild sepsis, as well as, in patients who died in contrast with those who survived [50]. The same phenomenon was determined in patients with burns, therefore TM might be useful to predict the course and severity of sepsis [51]. Nevertheless, further longitudinal studies are needed to confirm its clinical usefulness.

3.4. *ICAM and adhesion molecules*

It has been suggested that Intercellular adhesion molecule 1 (ICAM-1) is involved in the recruitment of Polymorphonuclear Leukocyte (PMNL) and secondary organ injury in response to inflammation and infection. The soluble ICAM-1 expression is upregulated during inflammation and in septic children the highest levels of ICAM-1 correlate with better outcomes [52].

Other soluble adhesion molecules have been associated with sepsis, specifically vascular cell adhesion molecule-1, P-selectin, L-selectin, and E-selectin. In a previous meta-analysis that enclosed the results of multiple studies, the increase of the levels of these adhesion molecules was consistent in septic patients of all ages (neonates, children and adults) [53]. This finding suggests a possible use of these novel molecules as markers of sepsis.

3.5. *Heat shock proteins (HSP)*

Heat shock proteins (HSP), as molecular chaperons, are a group of molecules that perform an important role in the host response to a wide variety of stresses that include environmental factors, oxidative damage, thermal damage, and infection, among others. Furthermore, HSP27, HSP60, HSP70 and HSP90 have demonstrated high expression in patients with sepsis; therefore, they could have a possible role as biomarker [54]. However, the information is still limited to being proposed as a specific marker for sepsis.

3.6. *Granzyme A and B*

Another candidate is Granzyme A (GZMA), this protein is a serine protease released by cytotoxic cells. In a previous study, plasma GZMA levels were decreased in septic rather than in non-septic burned patients and in healthy subjects. Furthermore, at day 3, plasma GZMA was significantly lower in non-survivor than in survivor patients with sepsis, indicating that this protein may serve as a possible marker of sepsis severity [55]. Granzyme B (GZMB) is another serine protease that is primarily produced by Cytotoxic T Lymphocyte (CTL) and Natural Killer Cells (NKC) and that is involved in CTL-directed target-cell apoptosis. GZMB expression has been correlated with the severity of sepsis, both in pediatric and adult patients. Due to this, GZMB levels form part in the panel of biomarkers that integrate the decision tree for management of septic shock [56].

3.7. *Monocyte chemo-attractant protein1 (MCP-1/CCL2)*

CCL2 is a chemokine that regulates the infiltration and migration of monocytes/macrophages. It is produced by a variety of cell types, either constitutively or after induction by cytokines, growth factors, or oxidative stress. In patients with sepsis, plasma levels of CCL2 in survivors and early death exhibited significant differences, indicating an imbalance of inflammation and anti-inflammation. This imbalance promoted overwhelming inflammation, leading to death [57]; therefore, CCL2 may be considered a promising biochemical marker.

3.8. *Metalloproteinases*

Matrix Metalloproteinases (MMP) are a family of zinc-containing proteinases that regulate matrix degradation and remodeling. MMP-8 and MMP-9 are released from granules in neutrophils when inflammatory stimuli are present. Altered levels of these proteins have been associated with sepsis development and outcome. Additionally, in a recent study, it was found that MMP-8 and MMP-9 levels were augmented in the early post-burn period in patients compared with healthy controls [58]. Therefore, these may be new candidates for burn-injury studies, and as new sepsis outcome biomarkers.

3.9. *Other biomarkers*

Adrenomedullin (ADM) is a 52 amino-acid peptide, and it possesses immunomodulating, metabolic, and vascular actions. The more stable Mid-Regional fragment of pro-adrenomedullin

(MR-proADM) could also be used as a marker of sepsis. This fragment comprises amino acids 45-92 and accurately reflects levels of the rapidly degraded active peptide. Furthermore, in a previous study, it was shown that values in healthy blood donors were lower (0.4 nmol/l) in comparison with individuals with sepsis (2.5 nmol/l) [59]. On the other hand, CD64 upregulation in neutrophils (nCD64) is thought to be an early step of the immune response to infection. nCD64 has been employed as a marker and it has demonstrated greater sensitivity than CRP and other hematological measurements for detecting sepsis or systemic infection [60]. A recent meta-analysis of eight different studies in adult patients with sepsis reveled the high specificity and sensitivity of nCD64 for the early diagnosis of sepsis [61].

4. Molecular markers

The Multi-Organ Failure (MOF) of critically burned patients causes multiple variations in protein and enzymatic levels in body fluids. Therefore, the development of strategies to find a group of sensitive and specific biomarkers is still underway; however, substantial progress has been already made and new possibilities are currently available. Fig. 1B depicts novel sepsis biomarkers in the “omics era” that are fundamental for determining the presence of sepsis in a burned patient with the necessary sensitivity to discriminate the patient’s general critical state from the development of sepsis. These markers are based on cellular responses to infection or sepsis, as well as on interindividual genomic variations; therefore, they could be the key in the future for better new specific biomarkers.

4.1. *Genomic DNA variations*

In recent years, diverse studies have identified genomic variants involved in sepsis and infectious susceptibility [62,63]. These studies have associated sepsis with polymorphisms localized in or adjacent to different genes, mainly in those involved in innate detection of pathogens or inflammation, such as *TLRs* [64], *CD14* [65–67], *cytokines* [68–71], *LBP* [72], *MMP* [73], *coagulation factors* [74,75] and others [76–78].

In respect to burns injury, several research groups have found polymorphisms associated with a higher risk of sepsis in burned patients [79–86] (See Table 2). Barber et al. reported in two articles that the Single Nucleotide Polymorphism (SNP) TLR4+896A/G is associated with a higher risk for severe sepsis [79,87]. In these studies, the authors analyzed 159 and 228 patients, respectively, and found that the TLR4+896 G-allele increased 1.8-fold the risk of developing severe sepsis after a burn injury, when compared with AA carriers [79,87]. Functional relevance for this SNP was suggested by previous studies, which demonstrated that G-allele carriers exhibited reduced responsiveness to LPS [88], as well as higher susceptibility to gram-negative sepsis and septic shock [88,89].

On the other hand, a relevant SNP at CD14 has been identified. A study suggested that the CD14-159C allele is associated with complicated sepsis in burned patients [87]. In agreement with this data, Barber et al. demonstrated that the CD14-159C allele increased at least 1.3-fold the risk of death after burn injury when compared to TT homozygotes [80]. The cytosine-to-thymine substitution affects the binding of Sp1, Sp2, and Sp3 transcription factors to the promoter of CD14, producing higher LPS-induced and constitutive transcription rates of CD14 for T-allele carriers than do C-allele carriers [90,91]. Therefore, this dysregulated transcription of the CD14 gene could explain the increased susceptibility of C-allele carriers.

An association study of cytokine genes revealed that TNF-α-308 G/A SNP is associated with severe sepsis following burn injury. This study revealed that carriers of the TNF-α- 308 A-allele had a higher risk of developing complicated sepsis when compared with GG homozygotes [86]. There is also evidence that the adenine-to-guanine substitution provokes an increase in the transcriptional regulation of TNF-α [92] which in turn, enhance the inflammatory response. IL-6 SNP were also investigated in association studies with sepsis in burned patients. These studies suggested that the IL-6-174C allele is associated with the risk of severe sepsis [87]. The IL-6-174C/G SNP is located within the promoter region and has been shown to regulate the transcription of IL-6 [93,94]. However, despite these evidences, recent meta-analyses evaluating the association of these SNPs with the risk of sepsis and mortality have challenged these findings because of controversial results between different research groups (Table 2) [95–97].

Therefore, it is necessary to carry out further studies with homogeneous criteria in order to identify potential confounding variables, to ensure the consistency of control samples, to properly design the study, and to have a suitable sample size. Likewise, each study should be adjusted to the genetic stratification of the studied population [119]. In addition, should be consider possible effects from other relevant factors, such as gene-gene or gene-environment interactions, as well as, molecular functional studies to demonstrate their role in the physio-pathogenesis of sepsis.

4.2. *Expression profiling*

Prior to the advent of genomic technology, efforts had been focused on the role of individual cytokines (e.g., FasL, IL-1, IL-6, IL-8, TNF-α) or a process such as apoptosis and cellular death in sepsis and organ failure following trauma [98]. It is clear that complications associated with burn injury and sepsis are highly complex and involves the cooperative action of diverse genes. Thus, genetic dissection of these pathological processes should be explored within a global context. In this respect, gene expression microarrays have provided comprehensive evidence of the transcription activities of virtually all genes simultaneously.

Several studies have employed microarray transcriptome methodology to identify potential genes associated with burn or sepsis, by using many tissues (including skin, cardiac and skeletal muscle, brain, liver, lung, kidney, spleen, and peripheral leukocytes), both in experimental models and in patients [99–101].

Circulating leukocytes have the ability to identify and mount an appropriate inflammatory response at the earliest sign of injury. qRT-PCR analysis has been used to confirm the gene expression patterns of potential biomarkers in the blood of presymptomatic individuals before the onset of clinical sepsis. Lukaszewski et al. in 2008 studied 92 patients at risk for developing sepsis at a critical care unit. These authors reported a neural network model based on the circulating levels of

Table 2 – Association studies between polymorphisms and outcomes of sepsis after burn injury.

Genes	Associated polymorphisms	Associations	Study design, sample size, and statistical analyses	References
IL-6 IL-10	IL-6-174G OR not specified IL-10-1082G OR not specified	IL-6-174G and IL-10-1082G alleles were associated with sepsis development in burned patients	Cohort study 71 patients and 109 healthy subjects Chi-square test, Fisher's exact test, logistic regression models (unspecified variables)	[79]
CD14	CD14-159C OR 2.9; 95% CI=1.25–6.80	Carriage of the CD14-159C allele was significantly associated with increased risk of mortality after burn injury, relative to TT homozygotes	Prospective cohort study 233 patients Multivariate analysis with adjustment for full-thickness burn size, inhalation injury, ethnicity, age and sex	[80]
CD14	CD14-159C OR 1.98; 95% CI=1.08–4.47	CD14-159C allele was associated with increased risk of mortality following burn injury	Prospective cohort study 149 patients Multivariate analysis adjusted for full-thickness, burn size, age, presence of inhalation injury, gender, and race/ethnicity	[81]
PAI-1	PAI-1 4G/4G OR not specified	The 4G/4G genotype of the 4G/5G promoter polymorphism of PAI-1 may be an important genetic risk factor of burn sepsis	Cohort study 182 patients Chi-square test (unadjusted analysis)	[82]
ND1	ND1-4216C OR=3.7; 95% CI=1.5–9.1; P=0.005	Carriage of the 4216C allele was associated with complicated sepsis, relative to carriers of the T allele	Cohort study 175 patients Multivariate analysis with adjustment for full-thickness burn size, inhalation injury, age, and sex	[83]
IL-10	IL-10-592A IL-10-819T OR 0.404; 95% CI=0.197–0.829	Carriage of IL-10-592A allele and IL-10-819T allele were associated with decreased risk for mortality after burn injury	Cohort study 265 patients and 31 healthy volunteers Multivariate analysis adjusted for age, percent of total body surface area, presence of inhalation injury, gender, and race/ethnicity	[84]
TNF-α	TNF-α-308A OR 10.7; 95% CI=1.2–95.5	TNF-α-308A variant allele was associated with increased risk of mortality after burn injury	Cohort study 69 patients Multivariate analysis adjusted for age, percent full-thickness burns, and inhalation injury	[85]
TLR4 TNF-α	TLR4+896G OR 6.4; 95% CI=1.77–23.17 TNF-α-308A OR 4.5; 95% CI=1.67–11.96	Carriage of the TLR4+896G-allele imparted increased risk of developing severe sepsis following a burn injury, relative to AA homozygotes. Carriage of the TNFα-308 A-allele imparted a similarly increased risk, relative to GG homozygotes.	Prospective cohort study 159 patients Multivariate analysis with adjustment for age, full-thickness burn size, ethnicity, and gender	[86]

(continued on next page)

Table 2 *(continued)*

Genes	Associated polymorphisms	Associations	Study design, sample size, and statistical analyses	References
TNF-α TLR4 CD14 IL-6	TNF-α-308A OR 2.6; 95% CI = 1.22 – 5.51 TLR4 + 896G OR 2.94; 95% CI = 1.13–7.66 CD14-159C OR 1.66; 95% CI = 1 2.76 IL-6-174C OR 2.25; 95% CI = 1.03–4.88	Alleles at TNF-α (308G), TLR4 (+896G), IL-6 (174C) and CD14 (159C) were significantly associated with an increased risk for severe sepsis after burn injury	Prospective cohort study 228 patients Multivariate analysis with adjustment for burn size, ethnicity, age, gender and inhalation injury	[87]

TLR4, Toll like receptor type 4; TNF-α, Tumor Necrosis Factor alpha; CD14, Cluster of differentiation 14; IL-6,Interleukin 6; IL-10, Interleukin 10; ND1, Nicotinamide adenine dinucleotide dehydrogenase 1; PAI-1, Plasminogen activator inhibitor-1; OR, Odds Ratio; CI, Confidence intervals.

mRNA from *CCL2*, *TNF-α*, *IL1*, *IL-6*, *IL-8*, *IL-10*, and *FasL* to predict which patients would develop sepsis. In this study, the authors accurately predicted the sepsis onset, with a 91.43% of sensitivity and 80.20% of selectivity, in more than 80% of patients between 4 and 1 days before a clinical diagnosis of sepsis was issued [102], so that, this network could be used as predictive tool for onset of sepsis, although further studies are needed.

Additionally, differences in gene expression between patients with SIRS who remained uninfected and patients who developed sepsis were evaluated by microarrays; 459 genes were differentially detected between the study groups, in which 14.2% were downregulated and 85.8%, upregulated. Altered genes were associated with cytokine receptors, the Mitogen-Activated Protein Kinase (*MAPK*) signaling pathway, the TLR pathway, the TH1/TH2 differentiation pathway, protein synthesis regulation, and the apoptosis pathway. Interestingly, these differences in gene expression were identified prior to the appearance of clinical changes; therefore, they may represent a useful diagnostic tool [103].

In a multicenter and prospective clinical trial that included patients with sepsis and healthy control individuals, transcriptional profiles in white blood cells were conducted to create a diagnostic guide for predicting sepsis outcomes, applying a set of 42 molecular biomarkers involved in extracellular remodeling, cell cycling, innate and adaptive immunity, leukocyte differentiation, and immune modulation pathways. Following validation by qPCR analysis, a specific gene expression profile associated with clinical features was proposed for detection of sepsis in early stages [104].

Only recently and in a mouse model, burn-induced sepsis has been studied at the genome level by high-throughput genomics technology facilitating comprehensive screening of biomarkers and allowing better understanding of the pathophysiological process. By applying a comparative microarray gene-expression approach, Xu et al. studied the Cecal Ligation and Puncture (CLP) mouse model of sepsis and, in addition, with a moderate burn, to identify specific genes associated with post-burn sepsis. In this study, *Acadm*, *Angptl4*, *Aqp8, Ehhadh*, *Gsta3*, *Gstm2*, *Gstt1*, *and Ppargc1a* were identified as potential gene biomarkers for sepsis [105]. After evaluation of pathway enrichment, authors hypothesized that the interactions among the *Acadm*, *Ehhadh*, *Angptl4*, *Ppargc1a*, and *Aqp8* genes could be associated with sepsis by means of the modulation of the mitochondrial function through the PPAR signaling pathway. They also assumed that *Gstt1*, *Gstm2*, and *Gsta3* might be involved in burn-induced sepsis through the glutathione metabolism pathway [105]. In a study conducted with the dual CLP and burned-model, gene expression data that involved a large number of liver transcriptional changes was documented. A set of important metabolic actors of gluconeogenesis, respiratory chain, amino-acid metabolism, and urea cycle were identified. In the same study, upregulation of transcript levels of glutamine and arginine transporters was found. Additionally, transcripts involved in lactate metabolism and key players of the pentose phosphate pathway were also observed. Pathways of the citric acid cycle, glycerol metabolism, and beta-oxidation were also identified [106]. Additional studies are needed in order to determine the feasibility of use of these molecules as biomarkers of burn sepsis in humans. However, this robust analysis is very promising to have a global perspective of alterations with greater sensitivity and specificity.

4.3. *Non-coding RNA markers*

MicroRNAs (miRNAs) are small noncoding RNAs 21–26 nucleotides in length, which act as posttranscriptional repressors that regulate gene expression [107]. Accumulating evidence has suggested that microRNAs are pivotal molecules that participate in the crosstalk between various pathways related to innate immunity, apoptosis, and mitochondrial functions [108]. Interestingly, recent studies have demonstrated the presence of miRNAs in human body fluids, such as whole blood, serum, plasma, sweat, urine, and cerebrospinal fluid [109,110], which opens the possibility of evaluating their clinical potential in accessible tissues; therefore, its role as a possible biomarker is feasible.

In previous studies, miRNA microarrays have been extensively used for miRNA expression profiling in patients with sepsis [111], and it was demonstrated that miRNA expression may be affected during various infectious pathologic processes [109]. Several studies have found that dysregulation of miRNA correlates with the symptomatology of serious inflammation and sepsis [112–117]. Some of these dysregulated miRNAs were associated with sepsis, including miR-25, miR-133a, miR-146, miR-150, and miR-223 [118]. This evidence has identified miRNAs that could be employed as efficient markers of different phases of sepsis. Vasilescu et al. showed an important down-regulated expression of miR150 in patients with early-stage sepsis [119]. Diverse miRNAs (miR-15a, miR16, miR-122, miR-146a, miR-223, and miR-499 5p) have been suggested as biomarkers for diagnosis, whereas miR-93b, miR-4835p, and miR-574-p could be utilized as prognostic biomarkers of sepsis [113,115,118,120]. Moreover, various miRNAs associated with exacerbated inflammatory response [116,121–125], immunosuppression, and apoptosis [126] could possess an important role in different phases of the sepsis process.

Notwithstanding multiple population characteristics, study designs, and normalization methodologies that could produce controversial results among studies, we demonstrated some of the most consistent and recently evaluated miRNA associated with sepsis in Table 3. The expression levels and potential role of these miRNA as biomarkers could be used in patients with burns, but it is necessary to perform validation studies in burn patients to develop efficient diagnostic tools.

Finally, recent studies have suggested an important role for long non-coding RNAs (IncRNAs) in various pathologies, including sepsis [127]. lncRNAs are more than 200 nucleotides in length and comprise a very heterogeneous group of molecules that play different cellular roles, such as mRNA stability, translation regulation, protein transport, RNA processing, among others. Recently, some *in-vitro* studies have reported the differential expression of lncRNA in monocytes, cardiomyocytes, and human tubular epithelial cells after exposure to LPS or the plasma of patients with sepsis [128,129]. In addition, it has been identified that lncRNAs play a role in the regulation of proinflammatory cytokines, Nuclear Factor-κB (NF-κB) signaling pathway, and other inflammatory and immune pathways, which may provide a novel method for the identification of sepsis [130]. In the same manner, the identification of circular RNAs (circRNAs) that are characterized by their stable circular structure could be used as biomarkers. The deregulation of circRNAs in sepsis has not, been studied to date; however, experimental knockdown of a RasGEF1B circRNA revealed the complex interaction of diverse cellular pathways in sepsis [131]. Therefore, employing different combinations on non-coding RNAs (miRNAs, lncRNAs and circRNAs) may be useful for developing a set of sensitive biomarkers of sepsis after burn injuries. These might comprise specific novel auxiliary markers, because these non-coding RNAs are sampled in a relatively noninvasive manner and are readily detected by RT-qPCR assay, a technique widely utilized in clinical laboratories.

4.4. *Epigenetic markers*

Recently, epigenetic studies have permitted the identification of biomarkers for several pathologies. Epigenetic modifications are heritable alterations that change the pattern of gene expression with no dependence on the DNA sequence. These alterations modify DNA accessibility and the chromatin structure through epigenetic markers such as DNA methylation and histone modifications, including phosphorylation, methylation, and acetylation, among others.

Previously, it was demonstrated that epigenetic modifications exert an effect on the regulation of the expression of key elements involved in sepsis and inflammation [132–134]. A genome-wide study in pediatric patients with septic shock demonstrated the deregulation of *HDAC1*, *EED, EZH2*, *RBBP4*, and *AEBP2* genes, which are involved in transcriptional repression via epigenetic regulation [135]. Additionally, several studies have reported the use of Histone Deacetylases Inhibitors (HDACI) to revert the molecular alterations produced by sepsis. For example, in a rodent sepsis model, the altered gene-expression profile identified by microarrays was partially restored by treatment with Suberoylanilidehydroxamic Acid (SAHA), a HDACI [136]. Although part of the HDACI effect on sepsis is due to the deacetylation of non-histone proteins, which in turn gives rise to alterations in expression or activity of key inflammatory regulators such as NF-κB and proinflamatory cytokines [137,138], important changes in histone acetylation patterns have also been observed. In a septic LPS-induced shock rodent model, a reduction in the acetylation pattern of H2A (H2AK5ac), H2B (H2BK5ac), and H3 (H3K9ac) histone proteins was described, and normal patterns were restored following administration of SAHA [137,164]. In contrast, in the CLP-induced sepsis mouse model, decreased levels of Class I HDAC were associated with increased acetylation of H3 and H4, and the treatment with the HDACI CG200745 was capable of preventing apoptosis in lung and spleen [139,166]. Further investigations are needed in order to study the presence of these epigenetics changes in human being, and to determine its possible use as predictors of the onset and prognosis of sepsis.

DNA methylation constitutes another important epigenetic marker implicated in the regulation of sepsis, in fact, it has been proposed as a novel epigenetic biomarker for bacterial sepsis. In this respect, a partial demethylated pattern of CpG sites in the promoter region of the bacterial- infection-responsive gene, Calcitonine-related polypeptide-α (*CALCA*), was detected in preterm neonates with sepsis but not in non-septic preterm neonates [140]. Consistent with this, altered DNA methylation patterns were observed in 64 genes including a group of PCDHB

Table 3 – miRNA expression during sepsis in human studies.

Expression	miRNA	Reference
Up-regulation in patients	miR-16/miR-15a	[112,115]
	miR-223	[113]
	miR-27a	[116]
	miR-133a	[172]
	miR-155	[173]
	miR-34a	[174]
	miR-143	[175]
Down-regulation in patients	miR-499-5p	[113]
	miR-25	[117]
	miR-150	[119,171]

genes (*PCDHB11*, *PCDHB12*, *PCDHB16*, *PCDHB5*, *PCDHB6*, *PCDHB7* and *PCDHB9*), *CCS* (Cooper Chaperone for Superoxide dismutase), and *DEGS2* (delta 4-desaturase sphingolipid 2) in newborns who developed sepsis. These genes are involved in the infectious response and inflammation [141]. Additional studies are required to evaluate the viability of using differential patterns of DNA methylations as possible epigenetics biomarkers of sepsis and especially in septic-burn patients. The knowledge of potential epigenetic biomarkers may provide a rationale of the physiological state of patients and the early diagnosis and prognosis of sepsis in burned patients.

4.5. *Advances in proteomics and metabolomics*

Proteomics, the high-throughput approach to protein expression analysis, is an additional method suitable for identifying biomarkers of sepsis. In 2009, Hattori and coworkers employed a proteomic strategy based on a combination of High-Performance Liquid Chromatography (HPLC) fractionation and one-dimensional electrophoresis coupled with Mass Spectrometry (MS) to analyze the serum of patients with sepsis. These authors identified 12 proteins whose level was increased, including Lipocalin 2, YKL-40, and S100A9, and 22 downregulated proteins including vitamin D-binding protein and the retinol-binding protein. It is noteworthy that the YKL-40 increase was further validated by additional assays that exhibited its potential as sepsis biomarker [142]. Recently, a 2-Dimensional Electrophoresis (2-DE) and MS study was executed in a cohort of 85 septic patients and 67 healthy donors. Six deregulated proteins were identified and the regulation of AntiThrombin-III (AT-III), CLUSterin (CLUS), and Serum Amyloid A-1 (SAA-1) was validated by Enzyme-Linked ImmunoSorbent assay (ELISA) [143]. In another report, a proteomic strategy based on 2-DE coupled with Matrix-Assisted Laser Desorption/Ionization-Time-of-Flight Mass Spectrometry (MALDI-TOF MS) was utilized for the identification of 11 differentially expressed proteins in lymphocytes of scalded and septic rabbits. Annexin I, Cyclophilin A, Cofilin, glutamate dehydrogenase, nucleoside diphosphate kinase, ubiquitin, and peroxyredoxins were identified among the altered proteins [144].

Metabolomics is a large-scale analysis of metabolites that can be applied to the study of biochemical events originating from burns and sepsis from virtually any biological fluid. When using this approach, low levels of free fatty acids, higher creatine concentrations, and altered activities of metabolites enzymes in serum from septic CLP rats were detected [145,146]. In another report, the metabolomics profile of plasma samples taken at admission to the critical care unit of severely injured patients was determined. Authors identified with certainty the development of sepsis during their hospitalization stay [147]. Interestingly, it was recently demonstrated that metabolomics and proteomics data could identify patients with septic shock from those undergoing a SIRS response in the absence of infection [148].

5. Future directions

A variety of pathophysiological changes take place after burn injury. Unfortunately, burn wounds are difficult to prevent, but the timely diagnosis of sepsis or of a high predisposition to develop severe infections may aid in choose the optimal treatment strategy [149]. Today, several molecular techniques, such as ELISA, fluorescence-based real-time detection, microarrays, MALDI-TOF MS, or Sanger sequencing have been proposed for rapid detection of pathogens. In addition, detection of cell-free DNA in blood as an indicator of severe sepsis can be achieved by using microfluidic devices capable of fast quantification of DNA in a small droplet ($< 10\,\mu l$) of whole blood and blood plasma in only 5 min [150]. Microfluidic devices are promising technologies for molecular diagnosis [151]. In recent years, some novel designs exploit the microorganism's properties, such as size, electrokinetic properties, and affinity. One of these protocols includes the use of a PDMS-based design to effectively lysate red blood cells and extract intact bacteria for downstream analysis [152]. Other microfluidic approaches include isolation and detection of changes in the electrical properties of leukocytes deriving from patients with sepsis [153]. The possibilities of patient DNA genome sequencing at a low cost by Next Generation Sequencing (NGS) platforms will offer the opportunity to evaluate the polymorphisms associated with a high risk of infection [154,155]. These studies have demonstrated high accuracy for detecting viruses, bacteria, and fungi among different samples [154]. Nonetheless, it also has some drawbacks, such as turnaround time, workflow, RNA virus detectability, and possible environmental contamination [155]. Probably, these new technologies will take greater relevance in the clinical-diagnostic area in the coming years.

6. Conclusions

Finally, the arrival of novel and powerful technologies in the — omics areas will not only provide better understanding of the complexity of the post-burn sepsis process, but will also lead to new diagnostic and prognostic tools that help to recognize the risk factors involved in a non-favorable clinical outcome. In summary, the search for new molecular biomarkers in combination with some traditional markers will be essential for the early detection of sepsis in patients with burns, and the new findings must be validated in this type of patient in order to create a sensitive, low-cost and time-effective diagnostic kit.

Conflicts of interest

The authors declare no conflict of interest. This work is consistent with the Journal's guidelines for ethical publication.

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