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The Relevance of Coding Gene Polymorphysms of Cytokines and Cellular Receptors in Sepsis

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Abstract

Sepsis is an injurious systemic host response to infection, which can often lead to septic shock and death. Recently, the immune-pathogenesis and genomics of sepsis have become a research topic focusing on the establishment of diagnostic and prognostic biomarkers. As yet, none have been identified as having the necessary specificity to be used independently of other factors in this respect. However the accumulation of current evidence regarding genetic variations, especially the single nucleotide polymorphisms (SNPs) of cytokines and other innate immunity determinants, partially explains the susceptibility and individual differences of patients with regard to the evolution of sepsis. This article outlines the role of genetic variation of some serum proteins which have the potential to be used as biomarker values in evaluating sepsis susceptibility and the progression of the condition.

Keywords: sepsis, biomarkers, cytokines, cell receptors, genes

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Introduction

Sepsis represents a severe and frequent complication of patients in intensive care units (ICU), with the potential of rapid development which can often lead to septic shock and death. On average the incidence of sepsis is of 300 cases/100,000 person-years, depending on the criteria used, geographic area and the studied period, with a high mortality of 20-50% [1-4].

The immune-pathogenesis and genomics of sepsis currently play a central role the biomedical research debate. It is anticipated that this will contribute to the development of meaningful diagnostic and prognostic algorithms in the optimisation of therapeutic decisions and disease prognosis [5].

Prompt diagnosis is the determining factor in optimising survival rates. At present, the accuracy of microbiological diagnostic tools is counterbalanced by their insufficient sensitivity.

The introduction in recent years of biomarkers (BM) as an additional diagnostic test has led to an improvement in both the achievement and rapidity of arriving at a diagnosis. By differentiating from other causes of systemic inflammatory response syndrome (SIRS), especially by exclusion, they facilitated a more accurate monitoring of the therapeutic response and a better estimate of the prognosis [5].

Diagnosis can be delayed because of difficulty in interpreting clinical features. Biomarkers have been shown to have a role as quantifiable indicators of normal biological processes or the presence and development of pathological processes. In recent years, the idea of sepsis biomarkers which can aid early diagnosis and the susceptibility of individuals has been established. However, none has the specificity necessary for the exclusive use, and it is currently accepted that a diagnosis of sepsis requires the identification of serum BM panels [6-8].

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Cytokines

The initial pro-inflammatory response is mediated by cytokines, soluble proteins with an integral role in the development of the immune response to infection. The cytokines validated as BM specific to the sepsis inflammatory immune-pathogenesis process, can be pro-inflammatory (tumour necrosis factor-alpha, interleukin-1, interleukin-6, interleukin-12, interferon-gamma, interleukin-8 and macrophage migration inhibitory factor) and anti-inflammatory (interleukin-10, interleukin-4 and transforming growth factor-beta) [9]. The alteration in cytokine expression and, subsequently, the poor functioning of host defence mechanisms is associated with the onset of sepsis. Lately, evidence has been gathered regarding genetic variations, especially the single nucleotide polymorphisms (SNPs) of cytokines and of other innate immunity determinants, which can partially explain the susceptibility and evolutionary differences in sepsis [10-17].

Tumour necrosis factor alpha

Tumour necrosis factor-alpha (TNF) is a protein rapidly released by activated immune cells after an infectious stimulus, serving as a trigger of the sepsis pro-inflammatory cascade. Elevated serum levels have been identified in septic shock [18,19]. Polymorphisms at positions -238, -308, -376 and +489, trigger an increase in serum TNF levels proportional to the severity of sepsis [14,20-22] and increases susceptibility to sepsis [16, 20-24]. The effect on prognosis is less certain [16,24].

Interleukin-6

Interleukin-6 (IL-6) is secreted mostly by hepatocytes, endothelial cells and fibroblasts [25]. It increases, at a hepatic level, the production of acute phase reactants (C-reactive protein – CRP), and at the bone marrow level, the production of circulating polymorphonuclear leukocytes (PMNs) [26]. IL-6 plays a key role in the systemic inflammatory response, elevated serum IL-6 levels being identified in severe forms of sepsis and correlated with increased mortality [22, 27-30].

The most studied SNP of IL6 is rs1800795 which leads to a G/C transition at the -174 promoter region. Although the G/C SNP at -174 influences the plasmatic levels of this BM, in sepsis the association is debated [25,31-33], with many studies reporting inconclusive results regarding the associated sepsis risk [14,22,24,34,35]. Others did not report significant associations, and Gao et. al. (2015) after conducting a meta-analysis, dismissed any association between increased levels and the risk of sepsis [25,36-40].

Interleukin-10

Interleukin-10 (IL-10), released by Th2 subgroup lymphocytes mediates the immune response by neutralising the proinflammatory action of IL-1 and TNF, having a subsequent protective effect on lipopolysaccharide-induced pathogeny. Elevated plasma levels indicate the presence of severe inflammation and correlation with severity and mortality in sepsis has been reported [41]. Recently, an increase in sepsis susceptibility and morbidity has been suggested by the presence of a promoter SNP for the -1082 polymorphism [34,41-44], although two meta-analyses confirmed the association only in an Asian population [45,46].

Stanilova et al. (2006) suggest that the -1082 G allele is associated with an increase in mortality and plasma IL-10 levels. On the other hand, Cardoso et al. (2015) demonstrated a decrease in its circulatory levels in individuals carrying the A allele, suggesting a pro-inflammatory effect and predisposition for septic shock of AA homozygotes [44,47].

Studies in which IL-10 is correlated with other, less studied, promoter SNPs (-819, -592) are necessary to verify those hypotheses [42,46,48].

Cellular receptors

Cellular receptors constitute a distinct BM category, having significance in all phases of the immune response.

Toll-like receptors (TLR)-4

Toll-like receptor (TLR) -4 is a receptor with a pro-inflammatory role, essential in the defence against Gram-negative bacteria, whose expression in peripheral blood, specifically in monocytes, is highly increased in sepsis [49]. It has been suggested that the altering of its expression through some SNPs +896 (rs4986790), -3725 (rs11536889), Asp299Gly has consequences on the development of sepsis and septic shock, sometimes being relevant only in combination with other polymorphisms [50-52].

Triggering receptor expressed on myeloid cells (TREM)-1

The soluble form of the triggering receptor expressed on myeloid cells (TREM)-1 is a member of the immu-

noglobulin family of receptors that are expressed on myeloid cells and act synergistically with TLR. TREM-1 is a BM with diagnostic performance and prognostic value [53-57]. The association between its genomic variability and sepsis is less defined. Peng et al. (2015) identified an increased susceptibility for septic shock of rs 223426, although the same SNP does not seem to modify the dynamic of plasma concentrations of the soluble form [55,56]; many authors denied the impact of SNPs in the development of sepsis (rs2234237, rs7768162, rs9471535) [56-59].

Cluster of differentiation (CD) -14

Cluster of differentiation (CD)-14 is a monocyte surface glycoprotein with an increased affinity for lipopolysaccharides which, in response to sepsis, releases its soluble component, presepsin. This is a sensitive and specific diagnostic BM in sepsis [60-62], while also being of prognostic value [60,63]. The C/T-159 (CD14-260) polymorphism in the promoter region has been associated with the risk of sepsis [43], although other authors refute the association [34,51,64]. However, Wang et al. (2014) identified a significant association of SNP rs2563298 with the risk for sepsis [51].

Plasminogen activator inhibitor (PAI)-1

Plasminogen activator inhibitor-1 (PAI-1) is a protein with a significant role in inhibiting fibrinolysis in sepsis, its serum concentrations being associated with the apparition of MSOF and septic shock. The involvement of the PAI-1 4G/5G polymorphism in increasing mortality due to sepsis has been suggested. However, the association of 4G/4G with increasing mortality due to sepsis has not been confirmed by other authors [65, 66], and the association between this mutation and elevated serum levels of PAI-1 is uncertain [67].

Soluble urokinase-type plasminogen activator receptor (suPAR)

Soluble urokinase-type plasminogen activator receptor is the soluble form, released through cleavage, of the receptor for the urokinase-type plasminogen activator (uPAR and CD87). It is expressed on immune cells such as granulocytes, activated lymphocytes, and macrophages, as well as endothelial and tumoral cells.

The pathogenic implications of an increase in suPAR have not been entirely elucidated. Its significance as a stable marker of inflammation subsequent to immune activation is generally accepted, having a good positive correlation with other markers of inflammation such as C-reactive protein (CRP), inflammatory cytokines, tumour necrosis factor alpha (TNF-alpha) and leucocytes [68,69]. Increased levels of serum suPAR have demonstrated in severe inflammatory conditions including tuberculosis, HIV infection, sepsis, as well as degenerative and neoplastic diseases [70]. Its role in reducing the inflammation induced by fibrinogen has been debated and is considered to be as an epiphenomenon in the inflammatory processes [70]. On the other hand, by inhibiting neutrophil efferocytosis [71], and implicitly compromising an adequate immune response in sepsis [72], it reflects more than a host immune dysfunction disorder [70]. Elevated levels in sepsis could mirror endothelial dysfunction [73].

The diagnostic contribution of suPAR in systemic infections is controversial. Its gradual increase in critically ill patients without SIRS compared to those with SIRS and sepsis is supported [73,74] but, despite its superior diagnostic value, not all studies report its correlation with CRP in sepsis [73,75]. An explanation could be the modest increase of suPAR under the influence of endotoxins, unlike PCT and CRP, whose increases are strongly induced by endotoxemia [76]. Huttunen (2011) does not confirm different suPAR levels in gram-negative bacteremia versus gram-positive bacteremia [77]. On the other hand, its diagnostic value is supported by Koch (2011) in patients with a pulmonary injury [78]. The independent predictive value of serum suPAR values referring to evolution/mortality has been supported by recent studies in patients with severe infections. Some authors substantiate its contribution as a prognostic BM in sepsis patient reporting 11 ng/mL as a predictive death value [74]. Retrospective [79] and prospective studies in patients with a bacteremia, identified suPAR as an independent predictor of mortality. Cut-off values have been associated with the severity of the disease, with a significance comparable to severity scores [77]. The reported results, referring to the prognostic value of suPAR compared to that of established severity scores (Acute Physiology and Chronic Health Evaluation - APACHE II, Sequential Organ Failure Assessment - SOFA, Simplified Acute Physiology Score - SAPS II), are not in complete agreement [73,75,80].

It should be mentioned that the studies evaluating suPAR are not very homogenous with regards to the selection of study groups, comorbidities, methods of measuring suPAR. The most important limitations in evaluating the utility of suPAR in predicting mortality

are the criteria used by authors to define bacteremia, Systemic Inflammatory Response Syndrome (SIRS) and sepsis [81].

Clinical applicability

Identifying the genetic variables of these biomarkers can lead to an individualized targeted therapy, but it can also identify situations of increased susceptibility, and example of which being the identification of the polymorphisms at -1641 AA, which encodes for protein C and which has been associated with organ dysfunction and an increase in sepsis mortality after the administration of activated protein C [81].

Although the methods allow for a risk stratification in sepsis and the develop of more specific, individualised therapies for various diseases, the limits are set by the difficulty in identifying all the functional and structural genetic variations. Further evaluations can be done through epigenetic studies such as modifications of DNA structure and transcriptomics, and quantifying mRNA or through proteomic confirmation of proteins [82].

The immune-pathogenesis and genomics of sepsis became central in the biomedical research debate. The improvement of the early diagnostic capacity and severity prognosis of sepsis by establishing a serum BM profile of the septic patient must be correlated with the severity of clinical forms of sepsis and septic shock.

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The authors report no conflicts of interest.

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