Journal of Infection (2015) 70, 445—456

BIAM British Infection Association

www.elsevierhealth.com/journals/jinf

Transcriptomic correlates of organ failure extent in sepsis

Raquel Almansa [a,b], María Heredia-Rodríguez [a,c], Esther Gomez-Sanchez [a,c], David Andaluz-Ojeda [a,d], Verónica Iglesias [a,b], Lucia Rico [a,b], Alicia Ortega [a,b], Estefanía Gomez-Pesquera [a,c], Pilar Liu [a,c], Marta Aragón [a,c], Jose Maria Eiros [e], Maria Ángeles Jiménez-Sousa [a,f], Salvador Resino [a,f], Ignacio Gómez-Herreras [a,c], Jesús F. Bermejo-Martín [a,b,*,g], Eduardo Tamayo [a,c,g]

[a] *Grupo de Investigación Biomédica en Cuidados Críticos (BioCritic), Hospital Clínico Universitario de Valladolid, SACYL/IECSYL, Avenida Ramón y Cajal, 3, 47005 Valladolid, Spain*
[b] *Unidad Apoyo a la Investigación, Hospital Clínico Universitario de Valladolid, SACYL/IECSYL, Avenida Ramón y Cajal, 3, 47005 Valladolid, Spain*
[c] *Servicio de Anestesiología, Hospital Clínico Universitario de Valladolid, SACYL, Avenida Ramón y Cajal, 3, 47005 Valladolid, Spain*
[d] *Servicio de Medicina Intensiva, Hospital Clínico Universitario de Valladolid, SACYL, Avenida Ramón y Cajal, 3, 47005 Valladolid, Spain*
[e] *Dpto de Microbiología, Universidad de Valladolid, Avenida Ramón y Cajal, 7, 47005 Valladolid, Spain*
[f] *Unidad de Infección Viral e Inmunidad, Centro Nacional de Microbiología — Instituto de Salud Carlos III, Carretera Majadahonda- Pozuelo km. 2, Majadahonda, 28220 Madrid, Spain*

Accepted 23 December 2014
Available online 31 December 2014

KEYWORDS
Sepsis;
Transcriptomics;

Summary *Objectives:* Sepsis is characterised by the frequent presence of organ failure and marked immunologic alterations. We studied the association between the extent of organ failure and the transcriptomic response of septic patients.

* Corresponding author. Unidad Apoyo a la Investigación, Hospital Clínico Universitario de Valladolid, SACYL/IECSYL, Avda Ramón y Cajal 3, 47005 Valladolid, Spain. Tel.: +34 983420000x383; fax: +34 983420040.
E-mail addresses: ralmansa@saludcastillayleon.es (R. Almansa), maria_her_05@hotmail.com (M. Heredia-Rodríguez), esthergzam@hotmail.com (E. Gomez-Sanchez), davidandaluz78@yahoo.es (D. Andaluz-Ojeda), viglesiasl@saludcastillayleon.es (V. Iglesias), lrico@saludcastillayleon.es (L. Rico), aortegaa@saludcastillayleon.es (A. Ortega), egp29@hotmail.com (E. Gomez-Pesquera), liupili@hotmail.com (P. Liu), mrt.aragon@gmail.com (M. Aragón), jmeirosbouza@gmail.com (J.M. Eiros), jimenezsousa@yahoo.es (M.Á. Jiménez-Sousa), salvador.resino@gmail.com (S. Resino), jgomez012001@yahoo.es (I. Gómez-Herreras), jfbermejo@saludcastillayleon.es (J.F. Bermejo-Martín), tamayo@med.uva.es (E. Tamayo).
[g] These authors contributed equally to this work.

http://dx.doi.org/10.1016/j.jinf.2014.12.010

Organ failure extent;
SOFA;
Immune response;
Immunosupression;
Microarrays

Methods: Gene expression profiles in the blood of 74 surgical patients with sepsis were compared with those of 30 surgical patients with no sepsis. Differentially expressed genes were assessed for their correlation with the sequential organ failure (SOFA) score.
Results: The expression levels of a group of genes participating in the cell cycle (HIST1H1C, CKS2, CCNA2, CDK1, CCNB2, CIT, CCNB1, AURKA, RAD51), neutrophil protease activity (ELANE, ADORA3, MPO, MMP8, CTSG), IL-1R and IL-18R response correlated directly with SOFA and mortality. Genes involved in T cell (LCK, CD3G, CD3D, ZAP70, ICOS, CD3E, CD28, IL2RB, CD8B, CD8A, CD40LG, IL23A, CCL5, SH2D1A, ITK, CD247, TBX21, GATA3, CCR7, LEF1, STAT4) and NK cell immunity (CD244, KLRK1, KLRD1) were inversely associated with SOFA and mortality.
Conclusions: The extent of organ failure in sepsis correlates directly with the existence of imbalanced innate and adaptive responses at the transcriptomic level. Quantification of the expression levels of the genes identified here could contribute to the simultaneous assessment of disease severity and immunological alterations in sepsis.

Introduction

Introduction

Sepsis is defined as a systemic inflammatory response to infection and is a major health problem in Europe and worldwide.[1] Sepsis occurs in approximately 2% of all hospitalised patients in developed countries.[2] Sepsis is frequently complicated by the presence of organ dysfunction, leading to severe sepsis and, in its most severe form, septic shock, which is characterised by persistent hypotension despite adequate fluid resuscitation.[3] In general, more than 50% of severe sepsis patients will require intensive care services (ICU).[2]

An evaluation of the extent of organ failure is mandatory in the management of septic patients because it provides a good indication of the patient's illness severity. This knowledge influences important clinical decisions, treatment, and prognosis. The extent of organ failure in septic patients is routinely evaluated using the sequential organ failure assessment (SOFA) score, which addresses the respiratory system, central nervous system, cardiovascular system, renal system, liver function and coagulation.[4,5] The SOFA score presents a good correlation to the ICU outcome, with mortality rates ranging from 3.2% in patients without organ failure to 91.3% in patients with failure of all six organs analysed.[6]

Sepsis is characterised by the presence of marked immunologic alterations that are linked to the existence of an important state of immunosupression that parallels this severe condition.[7] The degree of sepsis-associated immunosupression seems also to deeply influence the prognosis of this disease.[8] Interestingly, no previous works have evaluated the relationship between the extent of organ failure and the host immune response in sepsis. Gene expression analysis in the blood is a useful tool to study the host immune response to severe infections, including sepsis.[9–11] In this study, we performed a transcriptomic analysis to identify leucocyte-related expression signatures that are linked to disease severity in sepsis. We have identified a set of 55 genes that participate in the immune response to infection with expression levels that are closely associated to the SOFA score and prognosis in these patients.

Materials and methods

Study design

The EXPRESS study (Gene Expression in Sepsis) was an observational prospective study aimed at evaluating gene expression profiles in patients with sepsis performed at the surgical ICU of Hospital Clínico Universitario de Valladolid, Spain, from April 2012 to April 2013.

Patient selection

During the observation period, 104 patients undergoing surgery were recruited. Seventy-four of these patients presented with sepsis following the definition of the American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference,[3] while 30 patients showed Systemic Inflammatory Response Syndrome (SIRS) with no sepsis (control group). Fifteen healthy volunteers of similar ages to the patients were recruited from the staff of the Hospital Clínico Universitario de Valladolid, Spain for gene expression data normalisation. Approval of the study protocol for both the scientific and ethical aspects was obtained from the Scientific Committee for Clinical Research of Hospital Clinico Universitario, Valladolid, Spain. Informed consent was obtained directly from each patient or legal representative before enrolment.

Clinical data and treatment

A specific standard survey was employed to collect the clinical data, including medical history, physical examination and haematological, biochemical, radiological and microbiological investigations. Treatment decisions were not standardised for all patients but were made by the treating physician.

Microbial diagnosis

When infection was suspected, samples were extracted and sent to the Microbiology Service, where they were routinely Gram stained and cultured on general purpose media (blood agar, chocolate agar, and the differential media McConkey