

## COMMENTARY

# Interleukin-27: a potential new sepsis biomarker exposed through genome-wide transcriptional profiling

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See related research by Wong *et al.*, <http://ccforum.com/content/16/5/R213>

### Abstract

Sepsis is a complex clinical condition that is driven predominantly by deviations from the orderly stereotypic immunological response to infection. Much effort has been undertaken in the search for biomarkers that can assist in discriminating critically ill patients with sterile inflammation from those with sepsis. Such biomarkers may aid the clinician in therapeutic decision making upon admission of a patient. Interleukin-27 may be such a discriminative biomarker, as suggested in the previous issue of *Critical Care* by a study of critically ill children.

Sepsis is defined as the detrimental host response to infection, oftentimes accompanied by organ failure. Confirmation of infection in critically ill patients relies largely on culture results, a notoriously slow process. Additional, rapid tests, based on biomarkers that are specifically influenced by the presence of infection, may assist in the classification of patients. Biomarker discovery based on systemic molecular signatures represents a promising strategy.

The complex multifaceted properties of the host immune response preclude the sole use of reductionist approaches to define clinically useful molecular factors. In the previous issue of *Critical Care*, Wong and colleagues [1] leveraged the variability in genome-wide transcriptional profiles in whole-blood leukocytes of pediatric intensive care unit (ICU) patients at admission

to define differentially expressed genes between non-infectious critical illness (n = 21, negative bacterial culture) and sepsis (n = 60, positive bacterial culture). By considering a multiple-comparison adjusted significance threshold and selecting for those probes exhibiting at least twofold change in expression between median values of sepsis and non-infected patient groups, the authors identified 221 differentially expressed probes. The predictive performance of these probes to classify sepsis and non-infectious critical illness classes was put to the test by means of a leave-one-out cross-validation method. In this way, the authors correctly predicted 86% of the sepsis and non-infectious illness classes. Moreover, they assessed the top 100 classifier genes by means of a self-organizing map algorithm, visualized as a mosaic in the Gene Expression Dynamics Inspector platform, and used image analysis software to compare individual patient gene expression mosaics with two reference gene expression mosaics. On the basis of similarity of gene expression fit, individual patient mosaics were assigned to either non-infectious illness or sepsis classes. Using this strategy, the authors were able to achieve 90% specificity and 94% positive predictive value, thereby highlighting this list of 100 genes as candidate diagnostic biomarkers for bacterial infection in critically ill children. Epstein-Barr virus-induced gene 3 (*EBI3*), encoding a secreted glycoprotein that heterodimerizes with IL27p28 to form interleukin-27 (IL-27), presented the highest predictive power. By virtue of the high predictive power that was unmasked for *EBI3*, Wong and colleagues [1] subsequently validated their unbiased genomics-based discovery set by measuring serum levels of IL-27, although *IL27p28* was missing from their list of 100 predictive genes. Importantly, this was performed in a separate pediatric ICU cohort composed of 231 critically ill children, of whom 101 had a non-infectious illness and 130 met the sepsis criteria. The authors found that serum IL-27 concentrations were significantly higher in patients with sepsis in comparison with non-infected patients.

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Receiver operating characteristics yielded an area under the curve of 81.1%, and when a concentration threshold of at least 5 ng/mL was considered, IL-27 yielded 92% specificity and 91% positive predictive value for bacterial infection in critically ill children.

This interesting work highlights IL-27, a bioactive member of the IL-12 cytokine family, as a promising clinical biomarker for bacterial infection in critically ill children. The biological relevance of IL-27 in sepsis has been demonstrated in a mouse cecal ligation and puncture (CLP) model [2]. In this model, IL-27 was rapidly released into the circulation after CLP and, notably, *EBI3*<sup>-/-</sup> mice were protected from CLP-induced lethality. Moreover, neutralization of the IL-27/WSX-1 signaling axis by intraperitoneal injection of a soluble IL-27 receptor fusion protein protected mice from septic peritonitis-associated mortality [2]. Recently, in a study that was carried out in adult ICU patients and that further emphasized the importance of IL-27 for host immune reactions to bacterial infection, transcription of both IL-27 subunits, *EBI3* and *IL27p28*, was higher in septic patients with melioidosis and infections caused by other Gram-negative pathogens when compared with healthy controls, patients with type 2 diabetes, and patients with Gram-positive infection [3]. Interestingly, lower plasma IL-27p28 protein abundance was associated with survival from sepsis caused by melioidosis and other pathogens in the adult ICU [3].

Whole-genome transcriptional profiling of blood leukocytes represents an attractive tool to reveal biomarkers for diagnosis and risk stratification of patients with sepsis [4,5]. The study by Wong and colleagues [1] is an excellent example of how this unbiased molecular approach can be used to reveal protein biomarkers for sepsis. Transcriptional profiling or RNA sequencing or both could also be used to develop molecular biomarker tests [6,7]. Extensive validation in multiple independent cohorts of patients, the development of easy-to-use and reproducible assays, and subsequent testing in prospective clinical trials in which therapeutic decisions are

based on biomarker levels are warranted to establish the true value of sepsis biomarkers for clinical practice.

#### Abbreviations

CLP, cecal ligation and puncture; *EBI3*, Epstein-Barr virus-induced gene 3; ICU, intensive care unit; IL, interleukin.

#### Competing interests

The authors declare that they have no competing interests.

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