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EDITORIAL

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The long way of biomarkers: from bench to bedside

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Reliable biomarkers are very important for clinicians in bedside management, both as a diagnostic tool and as a follow-up of antibiotic therapy in patients with sepsis. Critical care researchers are currently facing two challenges with respect to the search for reliable biomarkers: (1) the biomarkers are to be integrated in different pathogenetic pathways of sepsis and (2) the diagnostic and prognostic values of the biomarkers are to be sensible. For instance, the hope that C-reactive protein (CRP) is a reliable prognostic marker in septic patients has now been challenged [1]. Similarly, the clinical utility of pro-calcitonin, either as a diagnostic or as a prognostic tool for systemic inflammation and sepsis, has brought contradictory results [2].

Long pentraxin 3 (PTX3) is a soluble pathogen pattern recognition receptor for innate immunity. Although both PTX3 and the CRP belong to the pentraxin family of acute phase proteins, PTX3 differs from CRP as it is directly released from the inflammation site by different cell types [3] and therefore reflects more the tissue injury than the host response. In other words, the expression of PTX3 may more directly present the status of distal organ injury than CRP, whose release is largely influenced by hepatic function. The gene expression of PTX3 was upregulated by a variety of stimulations, such as tumor necrosis factor-α (TNF-α), lipopolysaccharide (LPS), hemorrhagic shock/resuscitation and mechanical ventilation [4, 5], which is mediated through the JUN NH_2-terminal kinase (JNK) signaling pathway [6]. A couple of previous studies in patients with septic shock or with acute respiratory distress syndrome (ARDS) have shown an increased plasma level of PTX3 that was correlated with the severity of the diseases [7, 8]. These data suggest that PTX3 may serve as a biomarker in critically ill conditions.

Two studies by He et al. [9] and by Mauri et al. [10] published in this issue of Intensive Care Medicine were designed to test the validity of PTX3 as a biomarker in a mouse model of endotoxemia and in patients with sepsis. In the clinical study, 90 patients with severe sepsis or septic shock were enrolled [10, 11] where assays of available biomarkers and inflammatory mediators were conducted, and data were analyzed in relation to patient outcome. The investigators reported that the PTX3 levels remained elevated during the first 5 days after the diagnostic of sepsis, and thus it appeared to be a reliable prognostic marker; PTX3 levels had a better discriminative power for survival than those of CRP, IL-6 and TNF-α [10]. In the animal study [9], endotoxemia was introduced by intratracheal instillation of LPS in mice. After 24 h,

PTX3 protein in the bronchoalveolar lavage fluid was increased in parallel with the severity of lung injury.

Furthermore, tissue factor (TF), a key initiator of coagulation cascades, is highly expressed in patients with sepsis [12]. In the clinical study by Mauri et al. [10], the elevated expression of PTX3 was correlated with the activation of TF. In the animal study by He et al. [9], the mice challenged with LPS had increased TF activity that correlated with PTX3 expression. Treatment with anti-human TF monoclonal antibody dramatically attenuated the LPS-induced PTX3 expression, organ injury, alveolar fibrin deposition and inflammatory cell infiltration, indicating that the interplay between PTX3 and TF could be a potential mechanism that mediates sepsis and distal organ injury. Importantly, this study demonstrated that the expression of PTX3 reflected an effective therapeutic intervention, which supports that PTX3 is a biomarker for acute lung injury.

An NIH working group suggested that a good biomarker should reflect the pathogenic process of the disease and respond to a therapeutic intervention [13]. To achieve this goal, critical care researchers still have a long way ahead. Prior to clinical application, several issues will be addressed, including (1) the natural half-life of PTX3 in humans; (2) the time course of PTX3 expression at the protein level under antibiotic therapy; (3) the impact of sterile inflammation (surgery, pancreatitis, etc.) on PTX3 expression; (4) the effects of individual organ failure on the synthesis and clearance of PTX3; (5) the effects of insulin on PTX3 expression. A working hypothesis will be proposed based on the answers to these questions to form a powered prospective study for objective evaluation of using PTX3 as a biomarker.

Indeed, the exciting findings of the concentration of PTX3 being able to predict 3-month mortality after adjustment for major risk factors in patients with acute myocardial infarction [14], and to diagnose and evaluate the severity of non-alcoholic steatohepatitis [15] are encouraging. The use of PTX3 as a biomarker for heterogeneous and multi-organ syndromes, such as sepsis and ARDS, are yet to be established. Meanwhile, PTX3 should be considered as a research tool in the field of Intensive Care Medicine.

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