CRITICAL CARE

COMMENTARY

Why high suPAR is not super – diagnostic, prognostic and potential pathogenic properties of a novel biomarker in the ICU

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See related research by Backes *et al.*, http://ccforum.com/content/15/6/R270

Abstract

The soluble urokinase plasminogen activator receptor (suPAR) has been suggested as a biomarker that reflects immune cell activation. In critically ill patients, several independent investigations have reported elevated suPAR in conditions of systemic inflammatory response syndrome (SIRS), bacteriemia, sepsis, and septic shock, in which high circulating suPAR levels indicated an unfavorable prognosis. In a prospective cohort study in this issue of *Critical Care*, suPAR levels were detected in bronchoalveolar lavage (BAL) and identified inhalation injury. High systemic levels indicated an adverse prognosis. This study expands our knowledge of the diagnostic power of suPAR, confirms its prognostic value, and raises the demand for future studies investigating the pathogenic involvement of suPAR.

Inflammation is a key pathogenic factor in various conditions of critical illness, even in the absence of an infection. However, most of the biomarkers currently established in clinical practice are not sensitive enough to detect non-infectious states of inflammation early and reliably [1]. The urokinase plasminogen activator receptor (uPAR) is expressed on most leukocytes and is cleaved from the cell surface through inflammatory stimulation (Figure 1) [2]. The soluble uPAR, termed suPAR, has been suggested to mirror the degree of immunoactivation (Figure 1) and can be measured from blood, urine, saliva, or cerebrospinal fluid [3-5]. In this issue of *Critical Care*, Backes and colleagues [1] report, for the first time, that suPAR is also detectable in lung lavage fluid. In a prospective longitudinal cohort study of 26 patients (11 with and 15 without burn injury), the authors found that pulmonary suPAR levels were useful for the diagnosis of inhalation injury and that high systemic levels indicated an adverse prognosis in terms of duration of mechanical ventilation and length of intensive care unit (ICU) stay.

On the one hand, this study supports recent findings from several groups that circulating suPAR levels are valid biomarkers in determining the prognosis of critically ill patients in the ICU [6-9] and extends prior results to this specialized subset of ICU patients with burn injuries (Figure 1). On the other hand, this study suggests that the measurement of suPAR from bronchoalveolar lavage can serve as a specific tool for the diagnosis of inhalation trauma. The findings thereby challenge the current view that suPAR is a useful prognostic biomarker rather than a specific diagnostic biomarker [3]. This 'dogma' had been based on various studies investigating circulating suPAR levels in different disease etiologies, including sepsis, cardiovascular disorders, and cancer [6,10,11]. However, we could already demonstrate a diagnostic value of serum suPAR levels for identifying alcoholic etiology among patients with chronic liver diseases [12]. The paper by Backes and colleagues [1] indicates that suPAR measurements obtained from distinct body fluids, namely bronchoalveolar lavage, may be diagnostically important in the ICU setting. Nevertheless, before they can be applied to clinical routine, these results need to be validated in a larger cohort, which must include other pulmonary disorders such as pneumonia, non-infectious acute lung injury, and acute respiratory distress syndrome.

Another future direction of research should address the potential pathogenic role of elevated suPAR levels in different compartments because suPAR not only may be a valid biomarker but also may promote disease progression. Recently, suPAR has been mechanistically linked to the pathogenesis of focal segmental glomerulosclerosis.

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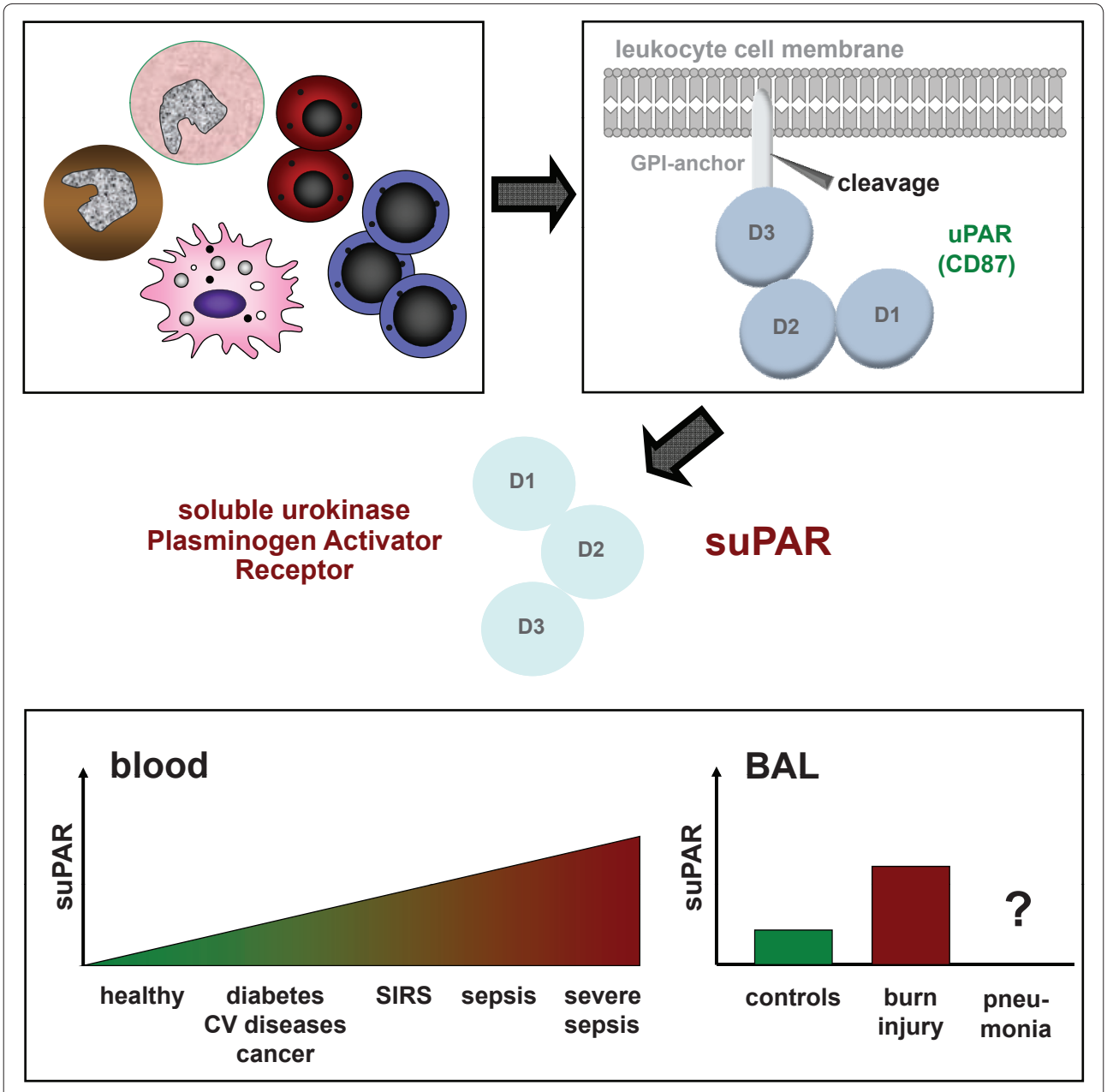

Figure 1. Schematic depiction of soluble urokinase plasminogen activator receptor (suPAR) as a novel biomarker in the intensive care unit. The urokinase plasminogen activator receptor (uPAR) (CD87) is expressed in various populations of immune cells, including neutrophils, monocytes, macrophages, and lymphocytes (upper left corner). uPAR consists of three disulphide-bonded domains (D1, D2, and D3) and is attached to the cell membrane by a glycosyl phosphatidylinositol (GPI) anchor. Domains D1 and D3 represent a composite binding site for uPA. Upon inflammation, the receptor is cleaved from the cell surface at the GPI anchor and is released into various body fluids (upper right corner). Circulating suPAR levels in serum are closely linked to inflammation in patients with type 2 diabetes, cardiovascular (CV) disorders, or cancer. The highest suPAR serum concentrations are found in critically ill patients with systemic inflammatory response syndrome (SIRS) or sepsis, and elevated suPAR values indicate an unfavorable prognosis (lower left corner). This was confirmed by Backes and colleagues [1] in a prospective observational cohort study of 26 intensive care unit patients (11 with and 15 without burn injury). As also demonstrated by the study, suPAR can be detected in bronchoalveolar lavage (BAL) and is indicative of inhalation injury (lower right corner). No data about pulmonary suPAR levels in pneumonia or other conditions of lung injury exist at present.

Circulating suPAR enters the glomerulus and binds β3 integrin, which normally anchors podocytes to the glomerular basement membrane [13]. Elevated plasma levels of suPAR lead to increased β3 integrin activation and consequently cause podocyte dysfunction and proteinuria. This cascade has been identified as a major promoting

pathogenic factor for renal scarring in focal segmental glomerulosclerosis [13]. Thus, it appears possible that elevated pulmonary suPAR in burn injury exerts directly chemotactic or other pro-inflammatory functions, thereby perpetuating inflammation and tissue damage. Future clinical studies and experimental animal models may therefore consider suPAR not only as an epiphenomenon but also as a potential therapeutic target in inflammatory disorders.

Abbreviations

ICU, intensive care unit; suPAR, soluble urokinase plasminogen activator receptor; uPAR, urokinase plasminogen activator receptor.

Competing interests

The authors declare that they have no competing interests.

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