

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), bacteremia, 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.

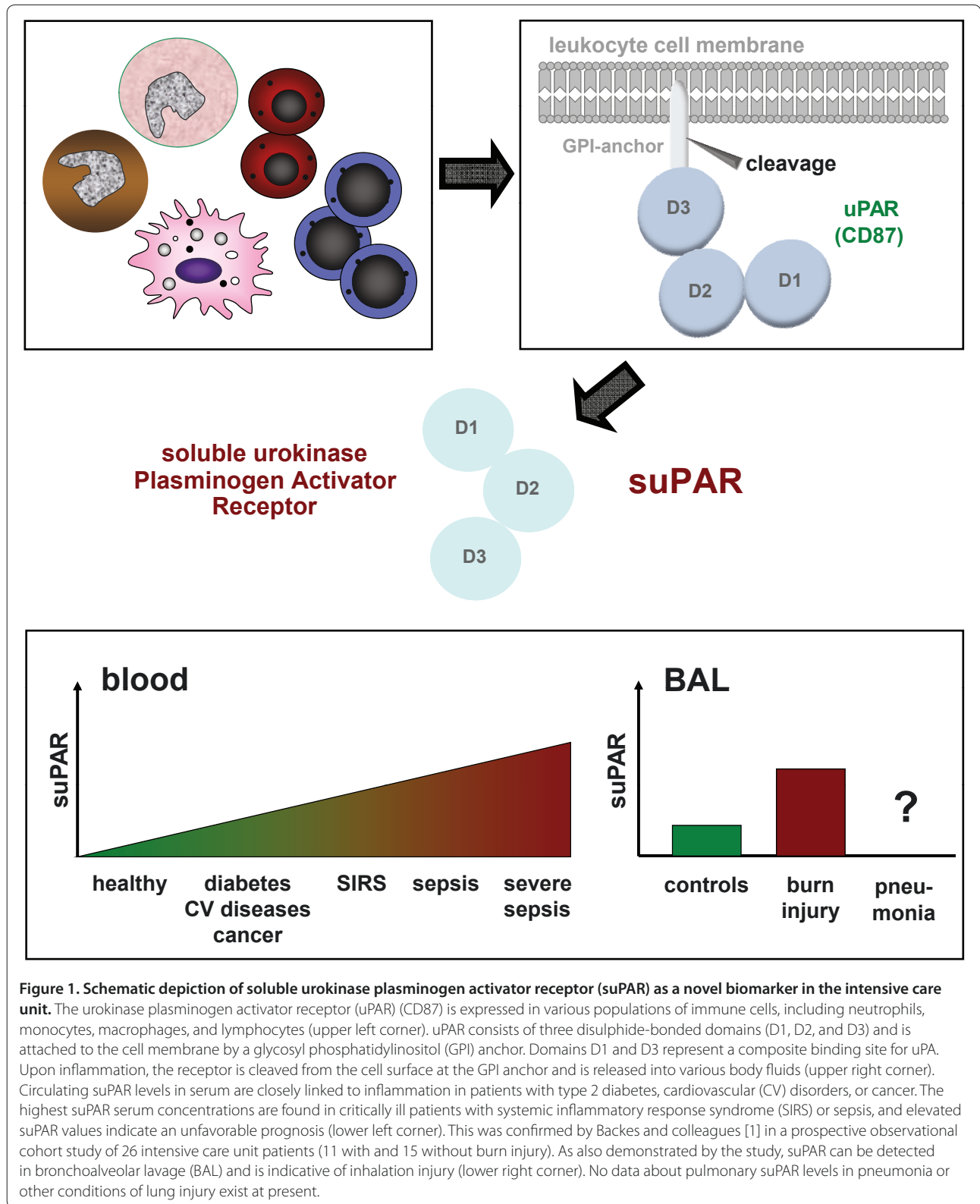
Inflammation is a key pathogenic factor in various conditions of critical illness, even in the absence of an infection. However, most of the biomarkers currently established in clinical practice are not sensitive enough to detect non-infectious states of inflammation early and reliably [1]. The urokinase 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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Circulating suPAR enters the glomerulus and binds $\beta 3$ integrin, which normally anchors podocytes to the glomerular basement membrane [13]. Elevated plasma levels

of suPAR lead to increased $\beta 3$ 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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References

1. Backes Y, van der Sluijs KF, Tuip de Boer AM, Hofstra JJ, Vlaar APJ, Determann RM, Knappe P, Mackie DP, Schultz MJ: **suPAR levels in patients with burn injuries and inhalation trauma requiring mechanical ventilation: an observational cohort-study.** *Crit Care* 2011, **15**:R270.
2. Blasi F, Carmeliet P: **uPAR: a versatile signalling orchestrator.** *Nat Rev Mol Cell Biol* 2002, **3**:932-943.
3. Eugen-Olsen J: **suPAR - a future risk marker.** *J Intern Med* 2011, **270**:29-31.
4. Rabna P, Andersen A, Wejse C, Oliveira I, Francisco Gomes V, Bonde Haaland M, Aaby P, Eugen-Olsen J: **Urine suPAR levels compared with plasma suPAR levels as predictors of post-consultation mortality risk among individuals assumed to be TB-negative: a prospective cohort study.** *Inflammation* 2010, **33**:374-380.
5. Tzanakaki G, Paparoupa M, Kyprianou M, Barbouni A, Eugen-Olsen J, Kourea-Kremastinou J: **Elevated soluble urokinase receptor values in CSF, age and bacterial meningitis infection are independent and additive risk factors of fatal outcome.** *Eur J Clin Microbiol Infect Dis* 2011 Oct 5. [Epub ahead of print].
6. Koch A, Voigt S, Kruschinski C, Sanson E, Duckers H, Horn A, Yagmur E, Zimmermann H, Trautwein C, Tacke F: **Circulating soluble urokinase plasminogen activator receptor is stably elevated during the first week of treatment in the intensive care unit and predicts mortality in critically ill patients.** *Crit Care* 2011, **15**:R63.
7. Savva A, Raftogiannis M, Baziaka F, Routsis C, Antonopoulou A, Koutoukas P, Tsaganos T, Kotanidou A, Apostolidou E, Giamarellos-Bourboulis EJ, Dimopoulos G: **Soluble urokinase plasminogen activator receptor (suPAR) for assessment of disease severity in ventilator-associated pneumonia and sepsis.** *J Infect* 2011, **63**:344-350.
8. Yilmaz G, Koksali I, Karahan SC, Mentese A: **The diagnostic and prognostic significance of soluble urokinase plasminogen activator receptor in systemic inflammatory response syndrome.** *Clin Biochem* 2011, **44**:1227-1230.
9. Huttunen R, Syrjanen J, Vuento R, Hurme M, Huhtala H, Laine J, Pessi T, Aittoniemi J: **Plasma level of soluble urokinase-type plasminogen activator receptor as a predictor of disease severity and case fatality in patients with bacteraemia: a prospective cohort study.** *J Intern Med* 2011, **270**:32-40.
10. Eugen-Olsen J, Andersen O, Linneberg A, Ladelund S, Hansen TW, Langkilde A, Petersen J, Pielak T, Møller LN, Jeppesen J, Lyngbaek S, Fenger M, Olsen MH, Hildebrandt PR, Borch-Johnsen K, Jørgensen T, Haugaard SB: **Circulating soluble urokinase plasminogen activator receptor predicts cancer, cardiovascular disease, diabetes and mortality in the general population.** *J Intern Med* 2010, **268**:296-308.
11. Langkilde A, Hansen TW, Ladelund S, Linneberg A, Andersen O, Haugaard SB, Jeppesen J, Eugen-Olsen J: **Increased plasma soluble uPAR level is a risk marker of respiratory cancer in initially cancer-free individuals.** *Cancer Epidemiol Biomarkers Prev* 2011, **20**:609-618.
12. Zimmermann HW, Koch A, Seidler S, Trautwein C, Tacke F: **Circulating soluble urokinase plasminogen activator is elevated in patients with chronic liver disease, discriminates stage and etiology of cirrhosis and predicts prognosis.** *Liver Int* 2011 Oct 17. [Epub ahead of print].
13. Wei C, El Hindi S, Li J, Fornoni A, Goes N, Sageshima J, Maiguel D, Karumanchi SA, Yap HK, Saleem M, Zhang Q, Nikolic B, Chaudhuri A, Daftarian P, Salido E, Torres A, Salifu M, Sarwal MM, Schaefer F, Morath C, Schwenger V, Zeier M, Gupta V, Roth D, Rastaldi MP, Burke G, Ruiz P, Reiser J: **Circulating urokinase receptor as a cause of focal segmental glomerulosclerosis.** *Nat Med* 2011, **17**:952-960.

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