ORIGINAL ARTICLE 10.1111/j.1469-0691.2004.00850.x

The plasma level of soluble urokinase receptor is elevated in patients with *Streptococcus pneumoniae* bacteraemia and predicts mortality

P. Wittenhagen[1], G. Kronborg[2], N. Weis[3], H. Nielsen[4], N. Obel[5], S. S. Pedersen[6] and J. Eugen-Olsen[1]

[1]Clinical Research Unit and [3]Department of Infectious Diseases, Copenhagen University Hospitals, Hvidovre, [2]Department of Infectious Diseases, Copenhagen University Hospitals, Rigshospitalet, [4]Department of Infectious Diseases, Aalborg Hospital, [5]Department of Infectious Diseases, Marselisborg Hospital, Aarhus, [6]Department of Infectious Diseases, Odense University Hospital, Denmark

ABSTRACT

This multicentre prospective study was conducted to investigate whether the level of the soluble form of urokinase-type plasminogen activator receptor (suPAR) is elevated during pneumococcal bacteraemia and is of predictive value in the early stage of the disease. Plasma levels of suPAR were increased significantly (median 5.5; range 2.4–21.0 ng/mL) in 141 patients with pneumococcal bacteraemia, compared to 31 healthy controls (median 2.6, range 1.5–4.0 ng/mL, p 0.001). Furthermore, suPAR levels were elevated significantly in patients who died from the infection ($n = 24$) compared to survivors ($n = 117$; $p < 0.001$). No correlation was found between suPAR levels and C-reactive protein. In univariate logistic regression analysis, hypotension, renal failure, cerebral symptoms and high serum concentrations of protein YKL-40 and suPAR were associated significantly with mortality ($p < 0.05$). In multivariate analysis, only suPAR remained a significant predictor of death (mortality rate of 13 for suPAR levels of > 10 ng/mL; 95% CI: 1.1–158). The increase in suPAR levels may reflect increased expression by vascular or inflammatory cells in the setting of pneumococcal sepsis. This plasma protein may be used to identify patients who are severely ill with pneumococcal bacteraemia.

Keywords Pneumococci, bacteraemia, suPAR, uPAR, prognostic marker, YKL-40

Original Submission: 26 November 2002; **Revised Submission:** 14 April 2003; **Accepted:** 24 April 2003

Clin Microbiol Infect 2004; 10: 409–415

INTRODUCTION

Streptococcus pneumoniae is the primary agent of community-acquired pneumonia [1] and is also associated with bacteraemia [2]. The annual incidence of pneumonia is estimated at 1–12/1000 population in developed countries [3]. Pneumococcal bacteraemia ranges from 9–18/100 000/year [4,5], with 17–36% mortality and the highest mortality amongst the elderly [6].

Urokinase-type plasminogen activator receptor (uPAR/CD87) is expressed on different cell types, including neutrophils, lymphocytes, macrophages, endothelial and malignant cells. uPAR and its ligand, urokinase-type plasminogen activator (uPA), are involved in numerous biological functions. In the pathogenesis of cancer, uPA and uPAR play a key role in tissue invasion by converting plasminogen into plasmin, leading to the degradation of extracellular matrix [7]. uPAR is able to bind β-integrins [8] promoting the migration of leukocytes [9]. uPAR can be cleaved from the cell surface by a number of proteases, such as chymotrypsin [10], phospholipase C [11] and uPA [12], to yield a soluble form of the receptor, suPAR. Proteolytic cleavage of uPAR from the cell surface can release a chemotactic active form of suPAR [13,14].

Recently, a strong correlation between the advanced disease state of HIV-1 infection and elevated suPAR levels was reported, suggesting the use of suPAR as a prognostic marker [15]. The reason for the strong prognostic value of suPAR in HIV infection is unknown, but binding of uPA to uPAR inhibits late stages of the HIV-1 life-cycle

Corresponding author and reprints requests: J. Eugen-Olsen, Clinical Research Unit 136, Copenhagen University Hospitals Hvidovre, Kettegaard Alle 30, 2650 Hvidovre, Denmark
E-mail: jeo@biobase.dk

in vitro [16,17]. suPAR has also been shown to be elevated and of prognostic value in patients with active pulmonary tuberculosis, and to be reduced following therapy [18].

The possible role of suPAR and uPA in immune responses to infectious diseases remains to be investigated. Gene knockout mice lacking uPAR have shown reduced pulmonary neutrophil recruitment and increased mortality to infection with *S. pneumoniae* compared to wild-type mice [19]. Up-regulation of uPAR on monocytes and leukocytes has been shown in experimental lipopolysaccharide endotoxaemia [20]. Lipoteichoic acid from *Streptococcus pyogenes*, as well as *Borrelia burgdorferi* surface proteins, facilitates monocyte uPAR and suPAR up-regulation *in vitro* [21].

Elevated serum levels of protein YKL-40, a lectin secreted from leukocytes, have been described during pneumonia [22], and Kronborg *et al*. [23] have shown that YKL-40 is an independent prognostic factor in pneumococcal bacteraemic patients. To our knowledge, besides YKL-40, only the APACHE II score has prognostic value for pneumonia, although this is limited [24]. The present study investigated whether the plasma suPAR level is elevated and associated with outcome in patients with *S. pneumoniae* bacteraemia.

Table 1. Age and sex distribution of the 141 patients included in the study and prognostic factors in *Streptococcus pneumoniae* bacteraemia. The table shows the mortality rate (MR) predicted by the different prognostic factors. All factors in the univariate logistic regression analysis were significant ($p < 0.05$). In the multivariate analysis, only suPAR levels above 10 ng/mL remained significant

Characteristic	n (died)	%	mortality (%)	
Age, years				
18–60	54 (6)	39	11	
61–75	50 (11)	35	22	
> 75	37 (7)	26	19	
Male	64 (13)	45	21	
Univariate analysis	n	MR	95% CI	p
Treatment of hypotension[a]	19 (6)	3.0	1.0–9.0	0.05
Cerebral symptoms[a,b]	41 (11)	2.9	1.1–7.4	0.03
Haemodialysis[a]	11 (6)	8.4	2.3–30.7	0.002
Alcoholism	21 (7)	3.0	1.0–8.5	0.04
YKL-40 level (ng/mL)				
0–200	29 (2)	1.0	–	–
201–500	30 (3)	1.5	0.2–9.0	0.6
≥ 501	30 (14)	11.8	2.4–58.8	0.003
suPAR level (ng/mL)				
0–5	64 (4)	1.0	–	–
5.1–10	55 (9)	3.0	0.8–10.1	0.08
≥ 10.1	19 (11)	20.6	5.3–80	0.0001
Multivariate analysis	n	MR	95% CI	p
Treatment of hypotension[a]	19 (6)	0.1	0–2	0.1
Cerebral symptoms[a,b]	41 (11)	3.7	0.8–17.1	0.09
Haemodialysis[a]	11 (6)	6.4	0.3–118	0.2
Alcoholism	21 (7)	0.8	0.2–6.2	0.8
YKL-40 level (ng/mL)				
0–200	29 (2)	1.0	–	–
201–500	30 (3)	0.8	0.08–7.9	0.8
≥ 501	30 (14)	3.9	0.4–35	0.2
suPAR level (ng/mL)				
0–5	64 (4)	1.0	–	–
5.1–10	55 (9)	2.2	0.3–16.8	0.4
≥ 10.1	19 (11)	13.0	1.1–158	0.04

[a]Data were only available for 139 patients.
[b]Cerebral symptoms were defined as unconsciousness or severe confusion at admission.
CI, Confidence Interval.

PATIENTS AND METHODS

Patients

Between October 1999 and June 2001, adults with *S. pneumoniae* bacteraemia admitted to one of five university hospitals (Aalborg, Aarhus, Odense, Hvidovre or Rigshospitalet) in Denmark were studied. Blood samples were taken on admission and clinical data were collected prospectively as described previously [25]. In total, 141 patients (77 female and 64 male) were included in the study (mean age 64 years; range 20–99 years). Most (66%) of the patients had an underlying illness: alcoholism ($n = 21$), chronic obstructive lung disease ($n = 18$), diabetes ($n = 13$), malignancy ($n = 19$), congestive cardiac disease ($n = 7$), HIV ($n = 1$) or others ($n = 13$). Pneumonia was the commonest type of infection ($n = 116$). Twenty-four patients died in hospital (case fatality rate of 17%); the cause of death was not determined systematically, but pneumococcal bacteraemia was considered to be the primary cause of death. Baseline characteristics of the patients are given in Table 1. All patients received appropriate antibiotic treatment, either from admission or from the point when the blood culture became positive (i.e., within the first 24 h). The control group consisted of 31 healthy individuals (laboratory workers; 27 male and four female; median age 49 years; range 31–63 years). The study was approved by the local Ethical Committees.

ELISA

Maxisorb plates (Nunc, Roskilde, Denmark) were coated and incubated overnight at 4 °C with 100 μL of murine monoclonal anti-suPAR antibody 2 μg/mL against human suPAR (kindly provided by Dr G. Hoyer-Hansen, Finsen Laboratory, Copenhagen, Denmark), diluted in coating buffer (15.1 mM Na_2CO_3, 35.7 mM $NaHC_3$, pH 9.6). Plates were washed with wash buffer (phosphate buffered saline (PBS) containing Tween 20 0.1% v/v) and blocked with SuperBlock (Pierce Chemicals, Dallas, TX, USA) diluted 1:1 in PBS. Plasma samples diluted in dilution buffer (7.3 mM KH_2PO_4, 50.7 mM Na_2HPO_4, 0.1 M NaCl, phenol red 0.5% w/w, pH 7.4) were added and the plates were incubated overnight at 4 °C. Bound suPAR was detected using 100 μL of rabbit anti-human suPAR polyclonal antibody 1.0 μg/mL (kindly provided by Dr G. Hoyer-Hansen) and mouse anti-rabbit polyclonal antibody conjugated with alkaline phosphatase (Sigma, St. Louis, MO, USA), diluted 1:2000. Each step was preceded by six washes with wash buffer, the antibodies were diluted in dilution buffer, and the plates were incubated for 1 h at 37 °C. Substrate (one tablet of *p*-nitrophenyl phosphate (Sigma) dissolved in 12 mL of 0.1 M Tris, 0.1 M NaCl, 5 mM $MgCl_2$, pH 9.5) was added to the wells and incubated at room temperature for 30 min. Reactions

were stopped by adding 50 μL of 1 M NaOH/well, and the absorbance was read at 405 nm. All ELISA measurements were carried out in duplicate. YKL-40 levels were measured by ELISA as described previously [23].

Statistics

Comparisons between groups were made with the Mann–Whitney U-test. When comparing suPAR levels in patients with underlying diseases, patients with multiple foci were excluded from the analysis. The use of suPAR as a prognostic marker was analysed using logistic regression analysis. p-values <0.05 were considered significant. All analyses were carried out using SPSS software (SPSS, Chicago, IL, USA).

RESULTS

The plasma level of suPAR was measurable in all 141 samples, with a median value of 5.5 ng/mL (range 2.4–21.0 ng/mL). The median level of suPAR in the control group was 2.6 ng/mL (range 1.5–4.0 ng/mL). The suPAR levels in the pneumococcal bacteraemic patients were significantly higher than in the healthy controls (Fig. 1a; p 0.001). The suPAR levels in patients with pneumonia ($n = 113$) as the single underlying disease were significantly higher (median 5.6; range 2.7-21.0 ng/mL) than in patients with otitis media or meningitis as the single underlying disease ($n = 22$; median 4.1; range 2.1–15.1 ng/mL; p 0.032); patients with multiple sites of infection were excluded. There was no correlation between suPAR levels and age ($r - 0.123$; p 0.15).

Significantly higher suPAR levels were measured in the patients who died ($n = 24$) compared to the survivors ($n = 117$) (Fig. 1b; p 0.0001). In the former group, 19 (79%) had suPAR levels above the median of 5.5 ng/mL. Fig. 2 shows the sensitivity and specificity of suPAR at different cut-off values.

The clinical parameters of prognostic importance in terms of death caused by the infection were cerebral symptoms (confusion, unconsciousness) at time of admission (p 0.03), hypotension (p 0.047) and kidney failure (p 0.002) (Table 1) [25]. The suPAR level was elevated significantly in patients with hypotension (p 0.0001) and renal failure (p 0.0001). The suPAR level was also elevated in the group of chronic alcohol abusers (p 0.0001). Underlying diseases were not associated significantly with a fatal outcome of pneumococcal bacteraemia, except for alcoholism (p 0.04).

C-reactive protein (CRP) was quantified in most ($n = 131$) of the patients. There was no

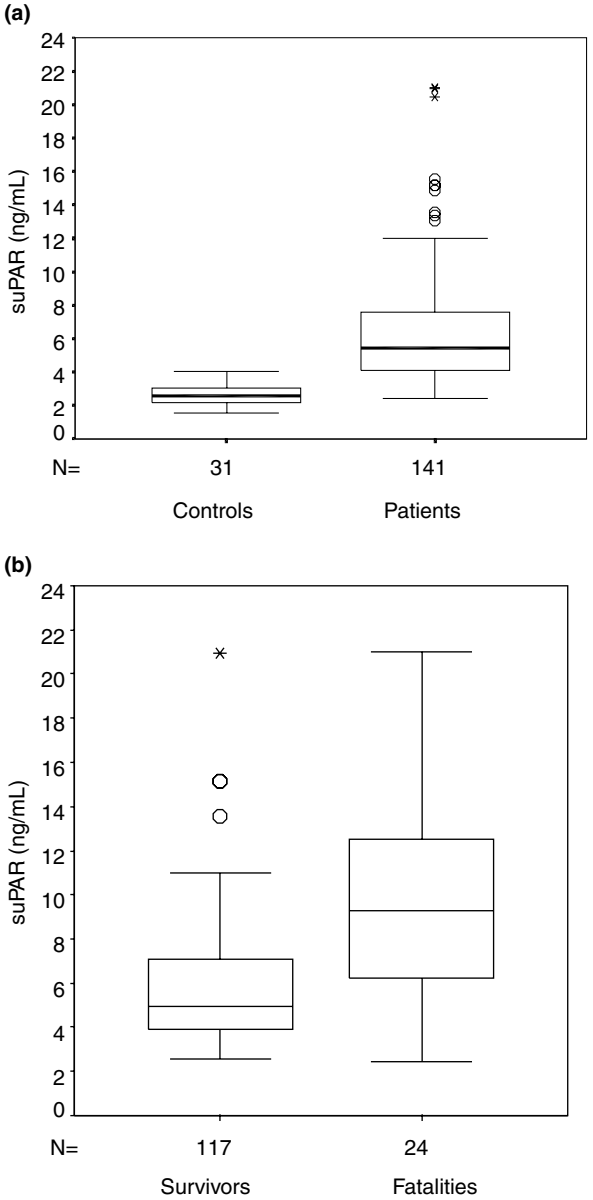

Fig. 1. Box plots based on the median, quartiles and extreme values of plasma suPAR levels. (a) Control group (median = 2.6 ng/mL) and pneumococcal bacteraemic patients (median = 5.5 ng/mL). The suPAR level was elevated significantly in patients compared to controls (p 0.001). (b) Patients surviving the infection (median = 5.0 ng/mL) and patients dying from the infection (median = 9.4 ng/mL). The increased level of suPAR in the group of fatilities was statistically significant (p 0.0001). The boxes represent the interquartile range that contains 50% of the values, with the highest and lowest values indicated, excluding outliers and extremes. Circles (o) represent outliers (1.5 and 3 box-lengths) and stars (*) represent extremes (values more than three box lengths).

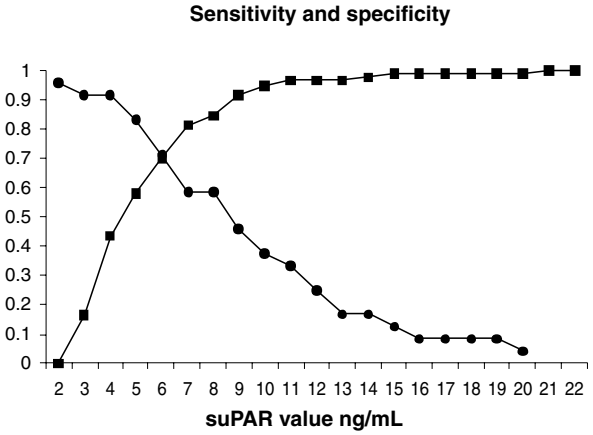

Fig. 2. Diagram showing sensitivity(●) and specificity (■) for each suPAR value. With a cut-off value of 10 ng/mL, the specificity was 0.95 and the sensitivity was 0.38.

correlation between suPAR levels and CRP levels (r – 0.004; p 0.96). High CRP levels were not prognostic of death. Neutrophils showed a weak but significant negative correlation to suPAR levels (Spearman rank correlation coefficient: – 0.237; p 0.006). When comparing suPAR levels with YKL-40 levels ($n = 89$), a strong correlation was identified between suPAR and YKL-40 (Spearman rank correlation coefficient: 0.70; p 0.0001).

In a logistic multivariate regression analysis (Table 1) that included all parameters found to be significant in univariate analysis (cerebral symptoms, mechanical ventilation, treatment of hypotension, renal failure, alcohol abuse and YKL-40), only the suPAR level remained associated significantly with death. The increase in mortality rate was 1.31/ng suPAR (95%CI: 1.10–1.57; p 0.0064). The suPAR levels ranged from 2.4 to 21.0 ng/mL. Patients with plasma suPAR levels of > 10 ng/mL had a mortality rate of 13 (p 0.04 compared to patients with suPAR levels between 0 and 5 ng/mL).

DISCUSSION

Studies have shown that uPAR knock-out mice have decreased neutrophil recruitment to the lung and increased mortality to pneumococcal pneumonia compared to wild-type mice [19]. Furthermore, the presence of uPAR is crucial for leukocyte adherence to the endothelium [26]. uPAR regulates cell migration; it can bind to β-integrins and may mediate cell–to–cell interaction and induce signal transduction [27]. However, cell migration in pneumococcal pneumonia is independent of binding β_2 integrins [19], suggesting the involvement of other mechanisms in uPAR-mediated migration. uPAR knock-out mice have shown similar results with respect to neutrophil recruitment during *Pseudomonas aeruginosa* infection, which is a β_2 integrin-dependent migration [28].

Mice lacking the uPAR ligand, uPA, have a possible increased immune response to *S. pneumoniae* [19]. Despite this, the absence of uPA in both *Cryptococcus neoformans* [29] and *Pneumocystis carinii* [30] infections in mice caused an impaired immune response. Lymphocyte recruitment to the lung was diminished in uPAR deficient mice, while recruitment was unaffected in uPA knock-out mice [31]. These observations suggest that uPAR is needed for neutrophil and lymphocyte recruitment, but that the mechanism is, at least partly, independent of proteolytic ability.

The present study demonstrated that suPAR levels are highly elevated and of prognostic value in patients with pneumococcal bacteraemia. Elevated suPAR levels have been shown previously to be of prognostic value for patients with various forms of malignant diseases [32–36], as well as with HIV-1 infection [15], urinary tract infection [37], tuberculosis infection [18], and bacterial meningitis [38]. Similarly, increased suPAR levels in the present study were a strong predictor of mortality. Other factors (see Results) were all of prognostic value, but only elevated suPAR levels were an independent predictor of mortality in multivariate logistic regression analysis. The strength of suPAR as a prognostic tool is illustrated in Fig. 2. With a cut-off value of 10 ng/mL, the specificity was 0.95, sensitivity was 0.38, the negative predictive value (NPV) was 0.88, and the positive predictive value (PPV) was 0.60. The high specificity and NPV should assist in identifying the large proportion of patients with a good prognosis. Hence, plasma suPAR levels could be used as a novel prognostic marker to identify high-risk patients.

It is difficult to compare suPAR values from different studies because of interassay variations and differences in the clinical conditions of the patients included. However, the very high elevations of suPAR levels found in the present study were similar to those found in urosepsis patients infected primarily by *Escherichia coli* [37], and

eight patients with bacterial meningitis infected by *S. pneumoniae* [38].

Evidence for the origin of plasma suPAR remains scarce. However, it is known that uPAR consists of three domains, and that proteolytic cleavage between domains 1 (D1) and 2 + 3 (D2D3) yields the active chemotactic domain D2D3 [13,14]. Proteolytic cleavage is mediated by both its own ligand, uPA [12], and by different proteases, e.g., chymotrypsin. The present study used a catching antibody of monoclonal anti-suPAR directed against domain 3 in the ELISA, thus detecting both intact suPAR and the chemotactic domain D2D3. During pneumococcal pneumonia, cytokines and different chemo-attractants are released, and increased mortality is associated with a high pulmonary interleukin-6 level [39]. Florquin *et al*. [37] found elevated suPAR levels in urosepsis patients, and suggested that suPAR was produced in the infected organ because of higher urine-to-plasma ratios and up-regulation of uPAR in the renal tubuli during infection. The elevated plasma suPAR levels seen in pneumococcal bacteraemia may be caused by increased secretion from leukocytes. Another source could be release of suPAR from vascular cells stimulated by cytokines, as shown by Chavakis *et al*. [40].

Elevated plasma suPAR levels have also been reported from a group ($n = 13$) of intensive care unit sepsis patients [41], suggesting that secretion of suPAR is increased during acute inflammation. In this study, suPAR and CRP levels were compared and no correlation was identified. This finding was supported by Slot *et al*. [42], who found no correlation between suPAR and CRP in patients with rheumatic diseases. However, suPAR levels are highly elevated in both *E. coli* sepsis and pneumococcal bacteraemia, suggesting an immunological response to severe infections.

The serum level of YKL-40, a matrix protein from neutrophils, has also been shown to be elevated during pneumonia and to decrease in response to therapy [22]. Patients from the present cohort also had elevated serum YKL-40 levels that were found to be an independent prognostic factor [23]. A positive correlation between suPAR and YKL-40 levels was identified. In the multivariate analysis, YKL-40 levels > 500 ng/mL, cerebral symptoms and haemodialysis were associated with an elevated mortality rate, but the associations were not significant. There was an inverse correlation between the number of neutrophils and suPAR levels, which may be explained by leukocyte depletion in severely ill patients.

Interestingly, lipopolysaccharide has been shown to up-regulate uPAR in monocytes and leukocytes, both *in vitro* and *in vivo* in healthy volunteers [20]. Surface proteins from *S. pyogenes*, *Salmonella typhimurium* and *B. burgdorferi* are also able to induce up-regulation of uPAR in monocytes and elevate suPAR *in vitro*. Thus, increased uPAR levels may be an immunological mechanism leading to increased cell migration in response to bacterial infections. As high suPAR levels are correlated with high uPAR levels [34], suPAR levels may be correlated with bacterial load and severity of the infection. Patients with pneumonia as the underlying disease had significantly higher suPAR levels compared to patients with other underlying diseases, despite equal mortality rates between these two groups. This difference might be explained by greater invasiveness of the infection in pneumonic patients, leading to a greater suPAR response. It remains to be determined whether suPAR levels decrease to normal levels following appropriate therapy, and thereby have the potential to become a treatment efficacy marker. The reported elevations in plasma suPAR levels during bacteraemia might reflect up-regulation of uPAR on neutrophils, monocytes and vascular cells, and indicate increased neutrophile and monocyte activity. The plasma suPAR level was elevated and was the only independent predictor of mortality in patients with pneumococcal bacteraemia. Hypotension, renal failure, cerebral symptoms, CRP and YKL-40 levels gave less or limited prognostic information. Measurement of suPAR levels may be useful for the clinical management of pneumococcal bacteraemia.

ACKNOWLEDGEMENTS

We would like to thank A-M. Meyer for skilled technical assistance and G. Hoyer-Hansen for providing antibodies.

REFERENCES

1. Macfarlane JT, Finch RG, Ward MJ *et al*. Hospital study of adult community-acquired pneumonia. *Lancet* 1982; **2**: 255–258.
2. Fang GD, Fine M, Orloff J *et al*. New and emerging etiologies for community-acquired pneumonia with implications for therapy. A prospective multicenter study of 359 cases. *Medicine* 1990; **69**: 307–316.

3. Marrie TJ. Community-acquired pneumonia: epidemiology, etiology, treatment. *Infect Dis Clin North Am* 1998; **12**: 723–740.
4. Nielsen SV, Henrichsen J. Incidence of invasive pneumococcal disease and distribution of capsular types of pneumococci in Denmark, 1989–94. *Epidemiol Infect* 1996; **117**: 411–416.
5. Sankilampi U, Herva E, Haikala R *et al.* Epidemiology of invasive *Streptococcus pneumoniae* infections in adults in Finland. *Epidemiol Infect* 1997; **118**: 7–15.
6. Balakrishnan I, Crook P, Morris R *et al.* Early predictors of mortality in pneumococcal bacteraemia. *J Infect* 2000; **40**: 256–261.
7. Dano K, Romer J, Nielsen BS *et al.* Cancer invasion and tissue remodeling – cooperation of protease systems and cell types. *APMIS* 1999; **107**: 120–127.
8. Wei Y, Lukashev M. Simon DI *et al.* Regulation of integrin function by the urokinase receptor. *Science* 1996; **273**: 1551–1555.
9. Chapman HA, Wei Y. Protease crosstalk with integrins: the urokinase receptor paradigm. *Thromb Haemost* 2001; **86**: 124–129.
10. Resnati M, Guttinger M, Valcamonica S *et al.* Proteolytic cleavage of the urokinase receptor substitutes for the agonist-induced chemotactic effect. *EMBO J* 1996; **15**: 1572–1582.
11. Asano S, Seishima M, Kitajima Y. Phosphatidylinositol-specific-phospholipase C cleaves urokinase plasminogen activator receptor from the cell surface and leads to inhibition of pemphigus-IgG-induced acantholysis in DJM-1 cells, a squamous cell carcinoma line. *Clin Exp Dermatol* 2001; **26**: 289–295.
12. Hoyer-Hansen G, Pessara U, Holm A *et al.* Urokinase-catalysed cleavage of the urokinase receptor requires an intact glycolipid anchor. *Biochem J* 2001; **358**: 673–679.
13. Fazioli F, Resnati M, Sidenius N *et al.* A urokinase-sensitive region of the human urokinase receptor is responsible for its chemotactic activity. *EMBO J* 1997; **16**: 7279–7286.
14. Resnati M, Pallavicini I, Wang JM *et al.* The fibrinolytic receptor for urokinase activates the G protein-coupled chemotactic receptor FPRL1/LXA4R. *Proc Natl Acad Sci USA* 2002; **99**: 1359–1364.
15. Sidenius N, Sier CF, Ullum H *et al.* Serum level of soluble urokinase-type plasminogen activator receptor is a strong and independent predictor of survival in human immunodeficiency virus infection. *Blood* 2000; **96**: 4091–4095.
16. Wada M, Wada NA, Shirono H *et al.* Amino-terminal fragment of urokinase-type plasminogen activator inhibits HIV-1 replication. *Biochem Biophys Res Commun* 2001; **284**: 346–351.
17. Alfano M, Sidenius N, Panzeri B *et al.* Urokinase-urokinase receptor interaction mediates an inhibitory signal for HIV-1 replication. *Proc Natl Acad Sci USA* 2002; **99**: 8862–8867.
18. Eugen-Olsen J, Gustafson P, Sidenius N *et al.* The serum level of soluble urokinase receptor is elevated in tuberculosis patients and predicts mortality during treatment: a community study from Guinea-Bissau. *Int J Tuberc Lung Dis* 2002; **6**: 686–692.
19. Rijneveld AW, Levi M, Florquin S *et al.* Urokinase receptor is necessary for adequate host defense against pneumococcal pneumonia. *J Immunol* 2002; **168**: 3507–3511.
20. Juffermans NP, Dekkers PE, Verbon A *et al.* Concurrent upregulation of urokinase plasminogen activator receptor and CD11b during tuberculosis and experimental endotoxemia. *Infect Immun* 2001; **69**: 5182–5185.
21. Coleman JL, Gebbia JA, Benach JL. *Borrelia burgdorferi* and other bacterial products induce expression and release of the urokinase receptor (CD87). *J Immunol* 2001; **166**: 473–480.
22. Nordenbaek C, Johansen JS, Junker P *et al.* YKL-40, a matrix protein of specific granules in neutrophils, is elevated in serum of patients with community-acquired pneumonia requiring hospitalization. *J Infect Dis* 1999; **180**: 1722–1726.
23. Kronborg G, Ostergaard C, Weis N *et al.* Serum level of YKL-40 is elevated in patients with *Streptococcus pneumoniae* bacteremia and is associated with the outcome of the disease. *Scand J Infect Dis* 2002; **34**: 323–326.
24. Brunkhorst FM, Al Nawas B, Krummenauer F *et al.* Procalcitonin, C-reactive protein and APACHE II score for risk evaluation in patients with severe pneumonia. *Clin Microbiol Infect* 2002; **8**: 93–100.
25. Kronborg G, Weis N, Madsen HO *et al.* Variant mannose-binding lectin alleles are not associated with susceptibility to or outcome of invasive pneumococcal infection in randomly included patients. *J Infect Dis* 2002; **185**: 1517–1520.
26. May AE, Kanse SM, Lund LR *et al.* Urokinase receptor (CD87) regulates leukocyte recruitment via beta 2 integrins in vivo. *J Exp Med* 1998; **188**: 1029–1037.
27. Tarui T, Mazar AP, Cines DB *et al.* Urokinase-type plasminogen activator receptor (CD87) is a ligand for integrins and mediates cell–cell interaction. *J Biol Chem* 2001; **276**: 3983–3990.
28. Gyetko MR, Sud S, Kendall T *et al.* Urokinase receptor-deficient mice have impaired neutrophil recruitment in response to pulmonary *Pseudomonas aeruginosa* infection. *J Immunol* 2000; **165**: 1513–1519.
29. Gyetko MR, Chen GH, McDonald RA *et al.* Urokinase is required for the pulmonary inflammatory response to *Cryptococcus neoformans*. A murine transgenic model. *J Clin Invest* 1996; **97**: 1818–1826.
30. Beck JM, Preston AM, Gyetko MR. Urokinase-type plasminogen activator in inflammatory cell recruitment and host defense against *Pneumocystis carinii* in mice. *Infect Immun* 1999; **67**: 879–884.
31. Gyetko MR, Sud S, Sonstein J *et al.* Antigen-driven lymphocyte recruitment to the lung is diminished in the absence of urokinase-type plasminogen activator (uPA) receptor, but is independent of uPA. *J Immunol* 2001; **167**: 5539–5542.
32. Fernebro E, Madsen RR, Ferno M *et al.* Prognostic importance of the soluble plasminogen activator receptor, suPAR, in plasma from rectal cancer patients. *Eur J Cancer* 2001; **37**: 486–491.
33. Gao W, Wang Z, Bai X *et al.* Detection of soluble urokinase receptor by immunoradiometric assay and its application in tumor patients. *Thromb Res* 2001; **102**: 25–31.
34. Mustjoki S, Sidenius N, Sier CF *et al.* Soluble urokinase receptor levels correlate with number of circulating tumor cells in acute myeloid leukemia and decrease rapidly during chemotherapy. *Cancer Res* 2000; **60**: 7126–7132.
35. Sier CF, Stephens R, Bizik J *et al.* The level of urokinase-type plasminogen activator receptor is increased in serum of ovarian cancer patients. *Cancer Res* 1998; **58**: 1843–1849.
36. Stephens RW, Pedersen AN, Nielsen HJ *et al.* ELISA determination of soluble urokinase receptor in blood from

healthy donors and cancer patients. *Clin Chem* 1997; **43**: 1868–1876.
37. Florquin S, van den Berg JG, Olszyna DP *et al.* Release of urokinase plasminogen activator receptor during urosepsis and endotoxemia. *Kidney Int* 2001; **59**: 2054–2061.
38. Winkler F, Kastenbauer S, Koedel U *et al.* Role of the urokinase plasminogen activator system in patients with bacterial meningitis. *Neurology* 2002; **59**: 1350–1355.
39. Dallaire F, Ouellet N, Bergeron Y *et al.* Microbiological and inflammatory factors associated with the development of pneumococcal pneumonia. *J Infect Dis* 2001; **184**: 292–300.
40. Chavakis T, Willuweit AK, Lupu F *et al.* Release of soluble urokinase receptor from vascular cells. *Thromb Haemost* 2001; **86**: 686–693.
41. Mizukami IF, Faulkner NE, Gyetko MR *et al.* Enzyme-linked immunoabsorbent assay detection of a soluble form of urokinase plasminogen activator receptor in vivo. *Blood* 1995; **86**: 203–211.
42. Slot O, Brunner N, Locht H *et al.* Soluble urokinase plasminogen activator receptor in plasma of patients with inflammatory rheumatic disorders: increased concentrations in rheumatoid arthritis. *Ann Rheum Dis* 1999; **58**: 488–492.