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Invited review:

Soluble urokinase plasminogen activator receptor - a valuable biomarker in systemic lupus erythematosus?

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Abstract

Systemic lupus erythematosus (SLE) is a potentially severe autoimmune condition with an unpredictable disease course, often with fluctuations in disease activity over time. Long term inflammation and drug-related side-effects may subsequently lead to permanent organ damage, a consequence which is intimately connected to decreased quality of life and mortality. New lupus biomarkers that convey information regarding inflammation and/or organ damage are thus warranted. Today, there is no clinical biomarker that indicates the risk of damage accrual. Herein we highlight the urokinase plasminogen activator receptor (uPAR) and especially its soluble form (suPAR) that besides having biological functions in e.g. proteolysis, cell migration and tissue homeostasis, recently has emerged as a promising biomarker of inflammation and prognosis of several disorders. A strong association between suPAR and organ damage in SLE was recently demonstrated, and preliminary data (presented in this review) suggests the possibility of a predictive value of suPAR blood levels. The involvement of suPAR in the pathogenesis of SLE remains obscure, but its effects in leukocyte recruitment, phagocytic uptake of dying cells (efferocytosis) and complement regulation suggests that central parts of the SLE pathogenesis could be regulated by suPAR, and *vice versa*.

Keywords

soluble urokinase plasminogen activator receptor (suPAR); systemic lupus erythematosus; organ damage; inflammation; biomarker; rheumatic disease; nephritis

Abbreviations: ACR, American college of rheumatology; ANA, antinuclear antibody; CHB, congenital heart block; CRP, C-reactive protein; GPI, glycosyl phosphatidylinositol; ECM, extracellular matrix; eGFR, estimated glomerular filtration; FSGS, focal segmental glomerulosclerosis; IL, interleukin; IFN α , interferon alpha; MMP, matrix metalloproteinase; NETs, neutrophil extracellular traps; OA, osteoarthritis; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; suPAR, soluble urokinase plasminogen activator receptor; SLICC, systemic lupus international collaborating clinics; SDI, SLICC/ACR damage index; SSA/Ro60, uPA, urokinase-type plasminogen activator; uPAR, urokinase plasminogen activator receptor

1. Background

The soluble form of the urokinase plasminogen activator receptor (uPAR/CD87) was recently evaluated as a serum biomarker in systemic lupus erythematosus (SLE), and elevated levels were found to correlate strongly with irreversible organ damage [1]. uPAR is a multi-ligand receptor, expressed on several cell types, and the receptor is involved in proteolysis, cell migration, angiogenesis and inflammation [2, 3]. Initial studies of soluble uPAR (suPAR) as a potential biomarker were performed in various forms of cancer where increased suPAR levels were associated with worse prognosis [2, 4]. Later, a substantial prognostic value of suPAR was demonstrated for infectious diseases such as HIV, tuberculosis, sepsis [5] and malaria [6-9]. Until today, suPAR has been evaluated as a biomarker of inflammation, organ damage and clinical outcome in numerous disorders including cardiovascular disease, hepatitis, renal disorders and rheumatic diseases [2, 10-13] but it was only recently studied in SLE [1, 14], a disease where reliable biomarkers of disease activity and organ damage are highly warranted [15].

SLE is a systemic rheumatic disease characterized by antinuclear antibody (ANA) production, increased expression of interferon alpha (IFN α) regulated genes, decrease in complement protein levels and deficient handling of dying cells which results in tissue deposition of immune complexes and subsequent inflammation and damage to organs [16, 17]. The disease can affect almost any organ and has an extreme heterogeneity which constitutes a challenge in the diagnosis and treatment of the patients. Further, the disease activity fluctuates over time with episodes of disease flares and remissions [18]. Although clinical symptoms and laboratory measurements such as autoantibodies, complement protein levels and blood cell counts can be merged into lupus disease activity scores (e.g. SLE disease activity index-2K), no single biomarker has yet been found to accurately mirror inflammation in each affected organ system [19]. C-reactive protein (CRP) which is frequently used to monitor systemic inflammation in various other conditions, is unfortunately not a reliable read-out of inflammation in SLE or viral infections, most likely due to an IFN α -dependent inhibition of hepatocyte CRP production [20, 21]. Another clinical challenge in SLE is to conveniently discriminate ongoing disease activity from irreversible organ damage. Such organ damage can be attributed to the disease itself, be a consequence of medication side-effects (e.g. long term corticosteroid use), or be related to comorbidities [22]. A validated tool for the assessment of accumulated organ damage is the Systemic Lupus International Collaboration Clinics/American College of Rheumatology damage index (SDI) [23]. The mortality of SLE is strongly associated with organ damage accrual and a reliable biomarker indicating or predicting such damage could thus improve treatment and survival of patients [15]. In this review we discuss the potential usefulness of

suPAR as a biomarker in SLE, and speculate regarding biological mechanisms of uPAR/suPAR that could be of relevance to the disease.

2. suPAR: distribution, structure and function

uPAR is a multi-ligand receptor expressed on many cell types including monocytes [24], activated T cells [25], neutrophils [26], tumor cells [27], megakaryocytes [28] and endothelial cells [29]. The receptor belongs to the lymphocyte antigen 6 (Ly-6) protein superfamily and is composed of three domains (D_I, D_{II} and D_{III}) of which D_{III} is attached to the plasma cell membrane via a glycosyl phosphatidylinositol anchor (GPI) (Figure 1). uPAR does not contain an intracellular domain and is therefore dependent on other receptors and molecules to mediate intracellular signaling. The involvement of uPAR in cell adhesion and migration is believed to be mediated via a complex interaction between urokinase-type plasminogen activator (uPA, also known as urokinase), low density lipoprotein receptor-related protein 1 (LRP1), vitronectin and integrins. A detailed description of these cooperative functions is given elsewhere [3, 30] and is only briefly described below.

Binding of uPA occurs primarily at the D_I domain of uPAR [31], and results in the cleavage of plasminogen to plasmin, a protease involved in fibrinolysis and tissue remodeling. The interaction between uPAR and integrins probably occur via the D_{II} and D_{III} domains [3]. Vitronectin, which is an extracellular matrix (ECM) protein [32], can bridge uPAR with β 3 integrins and thereby mediate a close and firm adhesion between integrins and ECM [3].

The expression of uPAR is mainly regulated by growth factors and pro-inflammatory cytokines like basic fibroblast growth factor, epidermal growth factor, tumor necrosis factor, interleukin (IL) -1 β and IL-6 [33-38] and the major formation of suPAR is mediated via shedding of uPAR from the plasma membrane. Although an alternative splicing of uPAR messenger RNA has been demonstrated, resulting also in synthesis of uPAR without a GPI-anchoring site [39], the relative impact of this suPAR source is unclear. Proteolytic cleavage sites are found between the D_I and D_{II} units of uPAR and at the GPI-anchor, rendering three possible soluble forms (full length D_I-D_{III}, D_{II}D_{III} and D_I, respectively) as well as two membrane-bound variants (full length and D_{II}D_{III}) (Figure 1). Enzymes responsible for cleavage of suPAR are uPA itself [40, 41], matrix metalloproteinases (MMPs) 3, 12, 19 and 25 [41], GPI-specific phospholipase D [42], neutrophil elastase [43], plasmin [40, 41, 44] and cathepsin G [43], of which the two latter enzymes are capable of cleaving at both sites (Figure 1). Factors that have been shown to induce suPAR shedding in an indirect way are cell-cell contact *per se* [45, 46], presence of pro-inflammatory cytokines [25, 47], bacterial lipopolysaccharide [46] and growth factors [47].

uPAR and suPAR are highly glycosylated proteins with molecular weights typically ranging between 55-60 kDa [48, 49]. The truncated D_{II}D_{III} form of suPAR has an approximate molecular weight range of 40-45 kDa and the D_I domain weight is around 16 kDa [50]. The biological functions of the different suPAR forms have not been fully revealed. D_I remains particularly obscure from a mechanistic perspective: it is found in urine [50], but remains undetectable in blood and other body fluids, possibly because of rapid serine proteinase-dependent degradation [43]. The D_{II}D_{III} fragment has distinct chemotactic properties due to a SRSRY motif in the linker region between the D_I and D_{II} domains that is exposed upon cleavage [51]. This fragment has been demonstrated to take part in stem cell mobilization [52] and leukocyte trafficking [26, 53, 54]. Full-length suPAR seems to retain both uPA as well as vitronectin-binding capacity [55, 56], but in contrast to cell-attached uPAR, full-length suPAR cannot be cleaved by uPA [57]. Due to this discrepancy, it has been speculated that suPAR could possibly retain uPA and vitronectin from cell bound uPAR and thereby inhibit uPA-uPAR-vitronectin mediated proteolysis, cell adhesion and migration [2].

3. suPAR as a clinical marker of inflammation and organ damage

Plasma membrane expression of uPAR as well as the levels of circulating suPAR have been investigated in relation to a broad range of conditions and suPAR has been referred to as a “molecular crystal ball” due to its prognostic value in diseases like tuberculosis, HIV, sepsis and cancer [2, 6, 13, 26, 58, 59]. Further, it has been reported that it reflects overall immune activation and systemic inflammation [2]. suPAR has also emerged as a potential biomarker of fibrosis in chronic liver diseases of diverse etiology [10, 11, 60-62].

Recently, suPAR attracted significant attention in primary focal segmental glomerulosclerosis (FSGS). This condition is characterized by damage to the podocytes, cells that are crucial for glomerular integrity, leading to massive proteinuria [63]. The etiology of FSGS is unknown, except in cases with genetic defects affecting the podocytes [63]. Wei *et al.* argued that suPAR is a causative factor of primary FSGS based on the finding that a majority of FSGS patients had inflammation-independent increased levels of suPAR, and that it, via β 3 integrins on podocytes, was shown to mediate effacement of podocyte protrusions [12]. However, the postulated central role and direct pathological action of suPAR in FSGS is debated intensively. Several studies report lack of differences in suPAR levels between FSGS and other kidney diseases and suggests rather a reduced glomerular filtration as a major cause of increased suPAR in patients with renal disorders [64-69].

suPAR is readily detected in both plasma and serum [50, 70] and it is also found in urine [50], cerebrospinal fluid [71] and saliva [72]. Blood levels of suPAR are dependent on age and sex [7] with slightly increased levels in elderly and females. However, circulating suPAR levels show relatively low circadian fluctuation, and are independent of body mass index [73] and hormone levels [74]. Further, blood and plasma levels of suPAR have been found to be highly stable *in vitro* even after repeated freeze-thaw cycles [75, 76] which increases its practical suitability as a biomarker candidate in clinical routine.

4. suPAR as a biomarker in SLE and other rheumatic diseases

In 1996, Belcher *et al.* reported that synovial fluid levels of suPAR were raised in patients with osteoarthritis (OA) and rheumatoid arthritis (RA) as compared to healthy controls [77]. Since then, uPAR and suPAR have been investigated both in humans and in animal models of OA [77-81], RA [26, 77, 78, 80, 82-88], gouty arthritis [89], and ankylosing spondylitis [90]. There are also observations on involvement of the uPAR system in systemic sclerosis [91-93] and Behçet's disease [94]. The first report on suPAR in SLE was presented by us as an abstract at the 2011 meeting of the American College of Rheumatology [1, 14]. This study comprised 198 patients with established SLE of which 19 were followed consecutively. Serum suPAR was not related to any disease activity measures, neither at a cross-sectional analysis, nor at an individual level in patients followed consecutively, and was not found to differ significantly from the levels found in 100 healthy controls [1, 14].

Subsequently, and contrasting to our findings Toldi *et al.* reported elevated suPAR in plasma from 89 SLE patients relative to healthy individuals, with a pronounced elevation of suPAR in patients with raised disease activity [95]. The diverging results may be explained by different study populations and that Toldi *et al.* did not adjust for age and sex [95], factors that are known to influence suPAR levels [7]. However, Qin *et al.* recently reported a weak association ($r=0.215$) between SLE disease activity and circulating suPAR [96]. At our laboratory, we continued by investigating the potential association between suPAR levels and accumulated organ damage in the previously mentioned group of patients [1]. Irreversible organ damage was recorded by the SDI, a damage index that covers 12 organ systems with well-defined manifestations; ocular, neuropsychiatric, renal, pulmonary, cardiovascular, peripheral vascular, gastrointestinal, musculoskeletal, skin, premature gonadal failure, diabetes and malignancy [23]. SDI is scored regardless of whether or not the damage can be attributed to SLE. In order to count, the index requires that damage must have occurred after the onset of SLE. Estimating SDI has proven clinically meaningful since the index score is highly correlated with prognosis and mortality [97-99]. The results revealed a strong and significant correlation between suPAR and SDI ($r=0.55$) [1]. This association remained strong after adjustment for age and

sex in a multiple regression analysis, and also after adjustment for other factors that could potentially influence suPAR levels (i.e. leukocyte count, platelet count and prednisolone dose). When dividing SDI into specific organ systems, we found a major impact of renal damage, and modest impact of ocular, neuropsychiatric, skin and peripheral vascular damage on suPAR levels [1]. The reason why other organ domains did not significantly associate with suPAR levels could possibly be that only a few patients scored in these domains. Another important aspect of this analysis is the differences in maximum possible score between the organ domains which range from 1 to 6, hence making some domains more prone to influence the regression model. New results from a Chinese lupus cohort support our findings by showing an association between suPAR levels and long-term renal outcome [96].

Our findings raised discussions regarding the potential value of suPAR as a *predictor* of organ damage and mortality among SLE patients. To investigate a possible predictive value of suPAR, the change in patient SDI between study inclusion (2008-2011) and 2013 was calculated and associated with suPAR levels at inclusion (details about patients are available in Enocsson *et al.* [1]). Previously unpublished data from this pilot study revealed significantly higher suPAR levels among patients with moderately or highly elevated SDI after study inclusion, compared to patients without SDI increase (Figure 2). Furthermore, there were higher death rates among patients in the two groups with SDI increase (Figure 2). However, it is well known that present organ damage predicts further organ damage [17, 100], and thus, adjustment for SDI at baseline should be performed to reduce the risk of bias. A stepwise linear multiple regression analysis was therefore performed to evaluate the impact of suPAR on future SDI increase. After adjusting for age, sex and SDI at study inclusion, we found suPAR levels to have a significant impact on future SDI increase ($p = 0.005$, standardized $\beta = 0.20$) whereas SDI at study inclusion was excluded from the model. Since recent studies have revealed an inverse correlation between serum suPAR and glomerular filtration [67, 68, 96], we also included estimated glomerular filtration (eGFR) (calculated by the 4-variable Modification of Diet in Renal Disease Study Group formula [101]) in the analysis, but eGFR was not retained in the model. From these results, we suggest that suPAR can actually predict organ damage independent of present SDI score or eGFR, but that a prospective study examining the association between suPAR levels at the time of diagnosis with future SDI would be preferable.

In line with these findings, elevated suPAR levels have previously been demonstrated to associate with the risk of developing cancer, cardiovascular disease and type 2 diabetes later in life in the general population [7]. Importantly, these associations were independent of CRP, which is known for its predictive value in cardiovascular disease [7, 102].

5. Potential roles of suPAR in SLE pathogenesis

Assessment of circulating suPAR levels at the clinical laboratory could possibly become a future way to estimate organ damage in SLE, and suPAR would be an even more appealing biomarker candidate if the levels could be mechanistically linked to the disease. The pathogenesis of SLE is notoriously complex and not fully understood, but includes disturbances in the waste disposal of dying cells with subsequent abnormalities in the classical complement activation pathway (or *vice versa*), dysregulation of the immune system leading to autoantibody production, immune complex formation and tissue deposition [18]. Organ damage in SLE, as defined by the SDI, originates from tissue inflammation (e.g. renal damage or pleural fibrosis) and from side-effects of medication, such as continuous corticosteroid use (e.g. cataract or osteoporosis), or long term use of immune suppression (e.g. infertility or malignancies) [103]. The biological mechanism(s) behind a correlation between suPAR and SDI is thus not obvious and needs considerable attention in future studies. However, there are a number of direct and indirect connections between uPAR/suPAR and key components of the SLE pathogenesis (outlined in Figure 3).

5.1 The complement system

A recent study by Amara *et al.* revealed substantial communication between the complement and coagulation systems; among factors involved in coagulation homeostasis, plasmin was shown to cleave both C3 and C5, generating biologically active anaphylatoxins C3a and C5a respectively [104]. Plasmin is generated from plasminogen by uPAR activation, and thus, uPAR/suPAR could indirectly affect the complement system resulting in inflammation and/or complement deficiency. However, we found no associations between serum C3 or C4 and suPAR levels in our cohort [1]. Furthermore the uPAR binding partner vitronectin [3, 32], which has been detected in complement and immune complex deposits of proliferative nephritis [105], is a regulator of the terminal complement pathway by binding C5b-9 [106].

5.2 Efferocytosis – the quiet elimination of dying cells

Since a defective clearance of dying cells is central in the SLE pathogenesis it is of interest to note that uPAR expression has been found to regulate efferocytosis [107-110], i.e. the phagocytic uptake of dying cells. Efficient efferocytosis prevents pro-inflammatory leakage of intracellular substances out of dying cells since these are taken care of before the membrane integrity is lost. Further, anti-inflammatory mediators and growth factors that can stimulate tissue repair are released upon efferocytosis [111]. In the context of organ damage it is most likely that an operational efferocytosis

would contribute to a controlled resolution of inflammation and a non-inflammatory remodelling of tissues.

A recent study demonstrated uPAR-dependent macrophage efferocytosis as well as accumulation of cell debris in the spleen of uPAR-deficient mice after being injected with apoptotic cells [110]. This uPAR-mediated efferocytosis required high molecular weight kininogen as a bridging molecule between phosphatidylserine (exposed on the apoptotic cell) and uPAR (on the phagocyte). In line with these results, there is another study reporting increased uptake of apoptotic T cells in uPAR overexpressing cancer cell lines [108]. Partly in contrast with these results, Park *et al.* demonstrated increased macrophage efferocytosis of apoptotic neutrophils when uPAR was knocked-out, either in the neutrophil or the macrophage, but interestingly not when knocked-out in both cell types [109]. A wide range of integrins were shown to be involved in this unilateral uPAR effect and the increased efferocytosis was reversed when exogenous suPAR was added to the experimental system [109]. The incomplete concordance of these studies can possibly be explained by differences between species as well as the cell types being professional versus non-professional phagocytes. Further, uPAR-regulated efferocytosis is most likely dependent on a complex cooperation between both soluble and cell-bound co-factors, making it difficult to define its precise role. Among the molecules that interact directly with uPAR/suPAR, vitronectin [112], plasminogen [113], plasminogen activator inhibitor-1 [114] and uPA [115] have all been implicated in the regulation of efferocytosis.

Based on a regulating role of uPAR in efferocytosis, Briassouli *et al.* investigated the role of uPAR in anti-SSA/Ro or anti-SSB/La mediated congenital heart block (CHB), a disorder that was recently suggested to involve incomplete clearance of apoptotic cardiocytes by viable cardiocytes [116]. Briassouli *et al.* found anti-SSA/Ro60 to up-regulate cardiocyte uPAR expression, and that this resulted in reduced efferocytosis and increased plasminogen activity [117]. Further, the augmentation of plasminogen activity resulted in transforming growth factor beta activation with a scarring phenotype of cardiac fibroblasts as a result [118]. In addition to increased uPAR expression on apoptotic cardiocytes, it has also been demonstrated that suPAR levels are increased in umbilical cord blood from children affected by CHB [119]. The effect of anti-SSA/Ro60 on uPAR expression on other cells than fetal cardiocytes has to our knowledge not been investigated, but if this effect is independent of cell type it could link suPAR levels to organ damage and dysfunction in SLE. Unpublished data from our group could not straight-forwardly verify increased serum levels of suPAR among SLE patients with anti-SSA/Ro60 (n=69) compared to patients without anti-SSA/Ro60 (n= 128), but it could also be argued that the autoantibodies would rather be removed from the circulation during such direct cell-activating interaction.

5.3 suPAR and neutrophils

The role of neutrophils in the pathogenesis of SLE is far from understood, but emerging data suggest an altered neutrophil phenotype and function in patients [120, 121]. The newly discovered form of neutrophil cell death, NETosis, in which neutrophils throw out chromatin fibers (neutrophil extracellular traps; NETs) containing antibacterial peptides and nuclear antigens, have been implicated in the SLE pathogenesis [121]. Increased NETosis [122] of SLE patients, as well as reduced capacity to degrade NETs have been demonstrated *in vitro* [123, 124]. It has also been suggested that dysfunctional neutrophils can contribute to organ damage [121]. In a recent study [125], Bengtsson and co-workers reported an association between organ damage (defined as SDI $\geq$ 1) and a reduced capacity of neutrophil granulocytes to mount an *ex vivo* intracellular respiratory burst following stimulation of protein kinase C. In the same study, it was also noted that SLE neutrophils showed a reduced expression of the chemoattractant receptor for complement fragment 5a (C5aR; CD88). Both findings are indicative of chemoattractant and NADPH oxidase activation of neutrophils in SLE. It is then interesting to note that there are several hypothetical routes by which suPAR could interfere with neutrophil migration, adhesion and activation:

- i) Elastase and cathepsin G, that are both readily released from activated neutrophils, are among the proteases known to participate in the formation of the various forms of suPAR (Figure 1);
- ii) The chemoattractant SRSRY-motif of the D_{II}D_{III} suPAR fragment can stimulate migration via the N-formyl-peptide receptor (FPR) [126] and the FPR-like-1 receptor FPRL1 [127], and the fragment could also be released from activated neutrophils [26, 53], and;
- iii) Interactions have been suggested between uPAR and the leukocyte cell adhesion receptor L-selectin (CD62L) [128], as well as between uPAR and the integrin complement receptor 3 [129], of which the latter receptor cooperates synergistically with the immunoglobulin G receptor Fc γ RIII (CD16) in triggering an efficient neutrophil oxidative burst [130].

We thus call for further analyses of neutrophil activation in relation to suPAR levels in general, and in SLE in particular.

6. Conclusions

The disease course in SLE is unpredictable with episodes of flares and remissions, sometimes leading to permanent organ damage and to preterm mortality [17, 131]. Many studies have shown that it is not, at any single occasion, raised disease activity that associates with poor prognosis and mortality,

but rather the acquired organ damage which is a product of medication side effects, comorbidities and disease activity over time. Apart from increased mortality, organ damage also implies a reduced physical function, quality of life and productivity for the patient [17]. Biomarkers with the potential to early identify individuals who are at risk of developing severe disease with subsequent organ damage are thus highly warranted. Data from our research group suggests a role of suPAR as a marker and a predictor of organ damage in SLE, but without explaining the underlying mechanisms. Given the growing number of reports on regulatory roles of suPAR regarding leukocyte recruitment and activation, efferocytosis and interaction with the complement system, it is tempting to speculate that altered suPAR levels might reflect dysregulation in the removal of apoptotic cells, which may result in inflammation as well as imbalance in tissue homeostasis and remodeling. However, many questions remain to be answered regarding the biological functions of suPAR, and its potential role as a clinical biomarker in SLE.

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Ethical statement

The SLE cohort was approved by the regional ethical review board in Linköping (Decision No. M75-08)

Conflicts of interest

None

References

1. Enocsson H, Wetterö J, Skogh T, Sjöwall C. Soluble urokinase plasminogen activator receptor levels reflect organ damage in systemic lupus erythematosus. *Transl Res* 2013;162:287-96.
2. Thuno M, Macho B, Eugen-Olsen J. suPAR: the molecular crystal ball. *Dis Markers* 2009;27:157-72.
3. Smith HW, Marshall CJ. Regulation of cell signalling by uPAR. *Nat Rev Mol Cell Biol* 2010;11:23-36.
4. Pappot H, Hoyer-Hansen G, Ronne E, Hansen HH, Brunner N, Dano K et al. Elevated plasma levels of urokinase plasminogen activator receptor in non-small cell lung cancer patients. *Eur J Cancer* 1997;33:867-72.
5. Backes Y, van der Sluijs KF, Mackie DP, Tacke F, Koch A, Tenhunen JJ et al. Usefulness of suPAR as a biological marker in patients with systemic inflammation or infection: a systematic review. *Intensive Care Med* 2012;38:1418-28.
6. Sidenius N, Sier CF, Ullum H, Pedersen BK, Lepri AC, Blasi F 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;96:4091-5.
7. Eugen-Olsen J, Andersen O, Linneberg A, Ladelund S, Hansen TW, Langkilde A et al. Circulating soluble urokinase plasminogen activator receptor predicts cancer, cardiovascular disease, diabetes and mortality in the general population. *J Intern Med* 2010;268:296-308.
8. Ostrowski SR, Ullum H, Goka BQ, Hoyer-Hansen G, Obeng-Adjei G, Pedersen BK et al. Plasma concentrations of soluble urokinase-type plasminogen activator receptor are increased in patients with malaria and are associated with a poor clinical or a fatal outcome. *J Infect Dis* 2005;191:1331-41.
9. Eugen-Olsen J, Gustafson P, Sidenius N, Fischer TK, Parner J, Aaby P 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;6:686-92.
10. Sjöwall C, Martinsson K, Cardell K, Ekstedt M, Kechagias S. Soluble urokinase plasminogen activator receptor levels are associated with severity of fibrosis in non-alcoholic fatty liver disease. *Trans Res* 2014;In press; doi: 10.1016/j.trsl.2014.09.007.
11. Berres ML, Schlosser B, Berg T, Trautwein C, Wasmuth HE. Soluble Urokinase Plasminogen Activator Receptor is Associated With Progressive Liver Fibrosis in Hepatitis C Infection. *J Clin Gastroenterol* 2012;46:334-8.

12. Wei C, El Hindi S, Li J, Fornoni A, Goes N, Sageshima J et al. Circulating urokinase receptor as a cause of focal segmental glomerulosclerosis. *Nat Med* 2011;17:952-60.
13. Sehestedt T, Lyngbaek S, Eugen-Olsen J, Jeppesen J, Andersen O, Hansen TW et al. Soluble urokinase plasminogen activator receptor is associated with subclinical organ damage and cardiovascular events. *Atherosclerosis* 2011;216:237-43.
14. Enocsson H, Wettero J, Skogh T, Sjowall C. Limited value of soluble urokinase plasminogen activator receptor as a disease activity marker in patients with systemic lupus erythematosus. *Arthritis Rheum* 2011;63:S556-S7.
15. Mak A, Isenberg DA, Lau CS. Global trends, potential mechanisms and early detection of organ damage in SLE. *Nat Rev Rheumatol* 2013;9:301-10.
16. Eloranta ML, Alm GV, Rönnblom L. Disease mechanisms in rheumatology--tools and pathways: plasmacytoid dendritic cells and their role in autoimmune rheumatic diseases. *Arthritis Rheum* 2013;65:853-63.
17. Bruce IN, O'Keefe AG, Farewell V, Hanly JG, Manzi S, Su L et al. Factors associated with damage accrual in patients with systemic lupus erythematosus: results from the Systemic Lupus International Collaborating Clinics (SLICC) Inception Cohort. *Ann Rheum Dis* 2014;In Press; doi: 10.1136/annrheumdis-2013-205171.
18. Munoz LE, Lauber K, Schiller M, Manfredi AA, Herrmann M. The role of defective clearance of apoptotic cells in systemic autoimmunity. *Nat Rev Rheumatol* 2010;6:280-9.
19. Ahearn JM, Liu CC, Kao AH, Manzi S. Biomarkers for systemic lupus erythematosus. *Transl Res* 2012;159:326-42.
20. Enocsson H, Sjowall C, Skogh T, Eloranta ML, Rönnblom L, Wetterö J. Interferon-alpha mediates suppression of C-reactive protein: Explanation for muted C-reactive protein response in lupus flares? *Arthritis Rheum* 2009;60:3755-60.
21. Enocsson H, Sjowall C, Kastbom A, Skogh T, Eloranta ML, Rönnblom L et al. Association of serum C-reactive protein levels with lupus disease activity in the absence of measurable interferon-alpha and a C-reactive protein gene variant. *Arthritis Rheumatol* 2014;66:1568-73.
22. Doria A, Gatto M, Zen M, Iaccarino L, Punzi L. Optimizing outcome in SLE: treating-to-target and definition of treatment goals. *Autoimmun Rev* 2014;In press; doi: 10.1016/j.autrev.2014.01.055.
23. Gladman D, Ginzler E, Goldsmith C, Fortin P, Liang M, Urowitz M et al. The development and initial validation of the Systemic Lupus International Collaborating Clinics/American College of Rheumatology damage index for systemic lupus erythematosus. *Arthritis Rheum* 1996;39:363-9.

24. Vassalli JD, Baccino D, Belin D. A cellular binding site for the Mr 55,000 form of the human plasminogen activator, urokinase. *J Cell Biol* 1985;100:86-92.
25. Nykjaer A, Moller B, Todd RF, 3rd, Christensen T, Andreasen PA, Gliemann J et al. Urokinase receptor. An activation antigen in human T lymphocytes. *J Immunol* 1994;152:505-16.
26. Pliyev BK, Menshikov MY. Release of the soluble urokinase-type plasminogen activator receptor (suPAR) by activated neutrophils in rheumatoid arthritis. *Inflammation* 2010;33:1-9.
27. de Bock CE, Wang Y. Clinical significance of urokinase-type plasminogen activator receptor (uPAR) expression in cancer. *Med Res Rev* 2004;24:13-39.
28. Wohn KD, Kanse SM, Deutsch V, Schmidt T, Eldor A, Preissner KT. The urokinase-receptor (CD87) is expressed in cells of the megakaryoblastic lineage. *Thromb Haemost* 1997;77:540-7.
29. Barnathan ES, Kuo A, Kariko K, Rosenfeld L, Murray SC, Behrendt N et al. Characterization of human endothelial cell urokinase-type plasminogen activator receptor protein and messenger RNA. *Blood* 1990;76:1795-806.
30. Czekay RP, Wilkins-Port CE, Higgins SP, Freytag J, Overstreet JM, Klein RM et al. PAI-1: An Integrator of Cell Signaling and Migration. *Int J Cell Biol* 2011;2011:562481.
31. Behrendt N, Ploug M, Patthy L, Houen G, Blasi F, Dano K. The ligand-binding domain of the cell surface receptor for urokinase-type plasminogen activator. *J Biol Chem* 1991;266:7842-7.
32. Wei Y, Waltz DA, Rao N, Drummond RJ, Rosenberg S, Chapman HA. Identification of the urokinase receptor as an adhesion receptor for vitronectin. *J Biol Chem* 1994;269:32380-8.
33. Reuning U, Bang NU. Regulation of the urokinase-type plasminogen activator receptor on vascular smooth muscle cells is under the control of thrombin and other mitogens. *Arterioscler Thromb* 1992;12:1161-70.
34. Pepper MS, Sappino AP, Stocklin R, Montesano R, Orci L, Vassalli JD. Upregulation of urokinase receptor expression on migrating endothelial cells. *J Cell Biol* 1993;122:673-84.
35. Koolwijk P, van Erck MG, de Vree WJ, Vermeer MA, Weich HA, Hanemaaijer R et al. Cooperative effect of TNF α , bFGF, and VEGF on the formation of tubular structures of human microvascular endothelial cells in a fibrin matrix. Role of urokinase activity. *J Cell Biol* 1996;132:1177-88.
36. Lund LR, Ellis V, Ronne E, Pyke C, Dano K. Transcriptional and post-transcriptional regulation of the receptor for urokinase-type plasminogen activator by cytokines and tumour promoters in the human lung carcinoma cell line A549. *Biochem J* 1995;310 (Pt 1):345-52.
37. Yoshida E, Tsuchiya K, Sugiki M, Sumi H, Mihara H, Maruyama M. Modulation of the receptor for urokinase-type plasminogen activator in macrophage-like U937 cells by inflammatory mediators. *Inflammation* 1996;20:319-26.

38. Florquin S, van den Berg JG, Olszyna DP, Claessen N, Opal SM, Weening JJ et al. Release of urokinase plasminogen activator receptor during urosepsis and endotoxemia. *Kidney Int* 2001;59:2054-61.
39. Pyke C, Eriksen J, Solberg H, Nielsen BS, Kristensen P, Lund LR et al. An alternatively spliced variant of mRNA for the human receptor for urokinase plasminogen activator. *FEBS Lett* 1993;326:69-74.
40. Hoyer-Hansen G, Ronne E, Solberg H, Behrendt N, Ploug M, Lund LR et al. Urokinase plasminogen activator cleaves its cell surface receptor releasing the ligand-binding domain. *J Biol Chem* 1992;267:18224-9.
41. Andolfo A, English WR, Resnati M, Murphy G, Blasi F, Sidenius N. Metalloproteases cleave the urokinase-type plasminogen activator receptor in the D1-D2 linker region and expose epitopes not present in the intact soluble receptor. *Thromb Haemost* 2002;88:298-306.
42. Wilhelm OG, Wilhelm S, Escott GM, Lutz V, Magdolen V, Schmitt M et al. Cellular glycosylphosphatidylinositol-specific phospholipase D regulates urokinase receptor shedding and cell surface expression. *J Cell Physiol* 1999;180:225-35.
43. Beaufort N, Leduc D, Rousselle JC, Magdolen V, Luther T, Namane A et al. Proteolytic regulation of the urokinase receptor/CD87 on monocytic cells by neutrophil elastase and cathepsin G. *J Immunol* 2004;172:540-9.
44. Beaufort N, Leduc D, Rousselle JC, Namane A, Chignard M, Pidard D. Plasmin cleaves the juxtamembrane domain and releases truncated species of the urokinase receptor (CD87) from human bronchial epithelial cells. *FEBS Lett* 2004;574:89-94.
45. Mustjoki S, Sidenius N, Vaheri A. Enhanced release of soluble urokinase receptor by endothelial cells in contact with peripheral blood cells. *FEBS Lett* 2000;486:237-42.
46. Koch A, Zimmermann HW, Gassler N, Jochum C, Weiskirchen R, Bruensing J et al. Clinical relevance and cellular source of elevated soluble urokinase plasminogen activator receptor (suPAR) in acute liver failure. *Liver Int* 2014;In press; doi: 10.1111/liv.12512.
47. Chavakis T, Willuweit AK, Lupu F, Preissner KT, Kanse SM. Release of soluble urokinase receptor from vascular cells. *Thromb Haemost* 2001;86:686-93.
48. Nielsen LS, Kellerman GM, Behrendt N, Picone R, Dano K, Blasi F. A 55,000-60,000 Mr receptor protein for urokinase-type plasminogen activator. Identification in human tumor cell lines and partial purification. *J Biol Chem* 1988;263:2358-63.
49. Behrendt N, Ronne E, Ploug M, Petri T, Lober D, Nielsen LS et al. The human receptor for urokinase plasminogen activator. NH₂-terminal amino acid sequence and glycosylation variants. *J Biol Chem* 1990;265:6453-60.

50. Sidenius N, Sier CF, Blasi F. Shedding and cleavage of the urokinase receptor (uPAR): identification and characterisation of uPAR fragments in vitro and in vivo. *FEBS Lett* 2000;475:52-6.
51. Fazioli F, Resnati M, Sidenius N, Higashimoto Y, Appella E, Blasi F. A urokinase-sensitive region of the human urokinase receptor is responsible for its chemotactic activity. *EMBO J* 1997;16:7279-86.
52. Selleri C, Montuori N, Ricci P, Visconte V, Carriero MV, Sidenius N et al. Involvement of the urokinase-type plasminogen activator receptor in hematopoietic stem cell mobilization. *Blood* 2005;105:2198-205.
53. Pliyev BK. Activated human neutrophils rapidly release the chemotactically active D2D3 form of the urokinase-type plasminogen activator receptor (uPAR/CD87). *Mol Cell Biochem* 2009;321:111-22.
54. de Paulis A, Montuori N, Prevete N, Fiorentino I, Rossi FW, Visconte V et al. Urokinase induces basophil chemotaxis through a urokinase receptor epitope that is an endogenous ligand for formyl peptide receptor-like 1 and -like 2. *J Immunol* 2004;173:5739-48.
55. Masucci MT, Pedersen N, Blasi F. A soluble, ligand binding mutant of the human urokinase plasminogen activator receptor. *J Biol Chem* 1991;266:8655-8.
56. Sidenius N, Andolfo A, Fesce R, Blasi F. Urokinase regulates vitronectin binding by controlling urokinase receptor oligomerization. *J Biol Chem* 2002;277:27982-90.
57. Hoyer-Hansen G, Pessara U, Holm A, Pass J, Weidle U, Dano K et al. Urokinase-catalysed cleavage of the urokinase receptor requires an intact glycolipid anchor. *Biochem J* 2001;358:673-9.
58. Sier CF, Stephens R, Bizik J, Mariani A, Bassan M, Pedersen N et al. The level of urokinase-type plasminogen activator receptor is increased in serum of ovarian cancer patients. *Cancer Res* 1998;58:1843-9.
59. Vasarhelyi B. Soluble urokinase plasminogen activator receptor, the candidate prophetic biomarker in severe inflammatory response syndrome. *J Intern Med* 2014;In press; doi: 10.1111/joim.12259.
60. 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 aetiology of cirrhosis and predicts prognosis. *Liver Int* 2012;32:500-9.
61. Andersen ES, Ruhwald M, Moessner B, Christensen PB, Andersen O, Eugen-Olsen J et al. Twelve potential fibrosis markers to differentiate mild liver fibrosis from cirrhosis in patients infected with chronic hepatitis C genotype 1. *Eur J Clin Microbiol Infect Dis* 2011;30:761-6.

62. Tuomi H, Kultti J, Danielsson J, Kangastupa P, Akerman K, Niemela O. Serum soluble urokinase plasminogen activator receptor in alcoholics: relation to liver disease severity, fibrogenesis and alcohol use. *J Gastroenterol Hepatol* 2014;In press; doi: 10.1111/jgh.12639.
63. Tryggvason K, Patrakka J, Wartiovaara J. Hereditary proteinuria syndromes and mechanisms of proteinuria. *N Engl J Med* 2006;354:1387-401.
64. Schlondorff D. Are serum suPAR determinations by current ELISA methodology reliable diagnostic biomarkers for FSGS? *Kidney Int* 2014;85:499-501.
65. Sinha A, Bajpai J, Saini S, Bhatia D, Gupta A, Puraswani M et al. Serum-soluble urokinase receptor levels do not distinguish focal segmental glomerulosclerosis from other causes of nephrotic syndrome in children. *Kidney Int* 2014;85:649-58.
66. Meijers B, Maas RJ, Sprangers B, Claes K, Poesen R, Bammens B et al. The soluble urokinase receptor is not a clinical marker for focal segmental glomerulosclerosis. *Kidney Int* 2014;85:636-40.
67. Harita Y, Ishizuka K, Tanego A, Sugawara N, Chikamoto H, Akioka Y et al. Decreased glomerular filtration as the primary factor of elevated circulating suPAR levels in focal segmental glomerulosclerosis. *Pediatr Nephrol* 2014;29:1553-60.
68. Musetti C, Quaglia M, Cena T, Chiocchetti A, Monti S, Clemente N et al. Circulating suPAR levels are affected by glomerular filtration rate and proteinuria in primary and secondary glomerulonephritis. *J Nephrol* 2014;In press; doi: 10.1007/s40620-014-0137-1.
69. Meijers BK, Reiser J. Reassessing the Reassessment of suPAR in Glomerular Disease. *Front Med (Lausanne)* 2014;1:59.
70. Stephens RW, Pedersen AN, Nielsen HJ, Hamers MJ, Hoyer-Hansen G, Ronne E et al. ELISA determination of soluble urokinase receptor in blood from healthy donors and cancer patients. *Clin Chem* 1997;43:1868-76.
71. Garcia-Monco JC, Coleman JL, Benach JL. Soluble urokinase receptor (uPAR, CD 87) is present in serum and cerebrospinal fluid in patients with neurologic diseases. *J Neuroimmunol* 2002;129:216-23.
72. Gustafsson A, Ajeti V, Ljunggren L. Detection of suPAR in the Saliva of Healthy Young Adults: Comparison with Plasma Levels. *Biomark Insights* 2011;6:119-25.
73. Andersen O, Eugen-Olsen J, Kofoed K, Iversen J, Haugaard SB. Soluble urokinase plasminogen activator receptor is a marker of dysmetabolism in HIV-infected patients receiving highly active antiretroviral therapy. *J Med Virol* 2008;80:209-16.
74. Guan YM, Carlberg M, Bruse C, Carlstrom K, Bergqvist A. Effects of hormones on uPA, PAI-1 and suPAR from cultured endometrial and ovarian endometriotic stromal cells. *Acta Obstet Gynecol Scand* 2002;81:389-97.

75. Riisbro R, Christensen IJ, Hogdall C, Brunner N, Hogdall E. Soluble urokinase plasminogen activator receptor measurements: influence of sample handling. *Int J Biol Markers* 2001;16:233-9.
76. Kofoed K, Schneider UV, Scheel T, Andersen O, Eugen-Olsen J. Development and validation of a multiplex add-on assay for sepsis biomarkers using xMAP technology. *Clin Chem* 2006;52:1284-93.
77. Belcher C, Fawthrop F, Bunning R, Doherty M. Plasminogen activators and their inhibitors in synovial fluids from normal, osteoarthritis, and rheumatoid arthritis knees. *Ann Rheum Dis* 1996;55:230-6.
78. Busso N, Peclat V, So A, Sappino AP. Plasminogen activation in synovial tissues: differences between normal, osteoarthritis, and rheumatoid arthritis joints. *Ann Rheum Dis* 1997;56:550-7.
79. Schwab W, Schulze-Tanzil G, Mobasheri A, Dressler J, Kotsch M, Shakibaei M. Interleukin-1 β -induced expression of the urokinase-type plasminogen activator receptor and its co-localization with MMPs in human articular chondrocytes. *Histol Histopathol* 2004;19:105-12.
80. Serrati S, Margheri F, Chilla A, Neumann E, Muller-Ladner U, Benucci M et al. Reduction of in vitro invasion and in vivo cartilage degradation in a SCID mouse model by loss of function of the fibrinolytic system of rheumatoid arthritis synovial fibroblasts. *Arthritis Rheum* 2011;63:2584-94.
81. Tang YL, Zhu GQ, Hu L, Zheng M, Zhang JY, Shi ZD et al. Effects of intra-articular administration of sodium hyaluronate on plasminogen activator system in temporomandibular joints with osteoarthritis. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2010;109:541-7.
82. Baran M, Mollers LN, Andersson S, Jonsson IM, Ekwall AK, Bjersing J et al. Survivin is an essential mediator of arthritis interacting with urokinase signalling. *J Cell Mol Med* 2009;13:3797-808.
83. Del Rosso A, Cinelli M, Guiducci S, Pignone A, Fibbi G, Margheri F et al. Deflazacort modulates the fibrinolytic pattern and reduces uPA-dependent chemoinvasion and proliferation in rheumatoid arthritis synoviocytes. *Rheumatology (Oxford)* 2005;44:1255-62.
84. Guiducci S, Del Rosso A, Cinelli M, Margheri F, D'Alessio S, Fibbi G et al. Rheumatoid synovial fibroblasts constitutively express the fibrinolytic pattern of invasive tumor-like cells. *Clin Exp Rheumatol* 2005;23:364-72.
85. Schwab W, Gavlik JM, Beichler T, Funk RH, Albrecht S, Magdolen V et al. Expression of the urokinase-type plasminogen activator receptor in human articular chondrocytes: association with caveolin and beta 1-integrin. *Histochem Cell Biol* 2001;115:317-23.

86. Slot O, Brunner N, Locht H, Oxholm P, Stephens RW. Soluble urokinase plasminogen activator receptor in plasma of patients with inflammatory rheumatic disorders: increased concentrations in rheumatoid arthritis. *Ann Rheum Dis* 1999;58:488-92.
87. Toldi G, Beko G, Kadar G, Macsai E, Kovacs L, Vasarhelyi B et al. Soluble urokinase plasminogen activator receptor (suPAR) in the assessment of inflammatory activity of rheumatoid arthritis patients in remission. *Clin Chem Lab Med* 2013;51:327-32.
88. Koga T, Okada A, Kawashiri S, Kita J, Suzuki T, Nakashima Y et al. Soluble urokinase plasminogen activator receptor as a useful biomarker to predict the response to adalimumab in patients with rheumatoid arthritis in a Japanese population. *Clin Exp Rheumatol* 2011;29:811-5.
89. Chu SC, Yang SF, Lue KH, Hsieh YS, Hsiao TY, Lu KH. Urokinase-type plasminogen activator, receptor, and inhibitor correlating with gelatinase-B (MMP-9) contribute to inflammation in gouty arthritis of the knee. *J Rheumatol* 2006;33:311-7.
90. Toldi G, Szalay B, Beko G, Kovacs L, Vasarhelyi B, Balog A. Plasma soluble urokinase plasminogen activator receptor (suPAR) levels in ankylosing spondylitis. *Joint Bone Spine* 2013;80:96-8.
91. D'Alessio S, Fibbi G, Cinelli M, Guiducci S, Del Rosso A, Margheri F et al. Matrix metalloproteinase 12-dependent cleavage of urokinase receptor in systemic sclerosis microvascular endothelial cells results in impaired angiogenesis. *Arthritis Rheum* 2004;50:3275-85.
92. Manetti M, Allanore Y, Revillod L, Fatini C, Guiducci S, Cuomo G et al. A genetic variation located in the promoter region of the UPAR (CD87) gene is associated with the vascular complications of systemic sclerosis. *Arthritis Rheum* 2011;63:247-56.
93. Margheri F, Manetti M, Serrati S, Nosi D, Pucci M, Matucci-Cerinic M et al. Domain 1 of the urokinase-type plasminogen activator receptor is required for its morphologic and functional, beta2 integrin-mediated connection with actin cytoskeleton in human microvascular endothelial cells: failure of association in systemic sclerosis endothelial cells. *Arthritis Rheum* 2006;54:3926-38.
94. Birengel S, Yalcindag FN, Yalcindag A, Sahli E, Batioglu F. Urokinase plasminogen activator receptor levels in Behcet's disease. *Thromb Res* 2011;128:274-6.
95. Toldi G, Szalay B, Beko G, Bocskai M, Deak M, Kovacs L et al. Plasma soluble urokinase plasminogen activator receptor (suPAR) levels in systemic lupus erythematosus. *Biomarkers* 2012;17:758-63.

96. Qin DD, Song D, Huang J, Yu F, Zhao MH. Plasma-soluble urokinase-type plasminogen activator receptor levels are associated with clinical and pathological activities in lupus nephritis: a large cohort study from China. *Lupus* 2014.
97. Nived O, Jönsen A, Bengtsson AA, Bengtsson C, Sturfelt G. High predictive value of the Systemic Lupus International Collaborating Clinics/American College of Rheumatology damage index for survival in systemic lupus erythematosus. *J Rheumatol* 2002;29:1398-400.
98. Rahman P, Gladman DD, Urowitz MB, Hallett D, Tam LS. Early damage as measured by the SLICC/ACR damage index is a predictor of mortality in systemic lupus erythematosus. *Lupus* 2001;10:93-6.
99. Stoll T, Seifert B, Isenberg DA. SLICC/ACR Damage Index is valid, and renal and pulmonary organ scores are predictors of severe outcome in patients with systemic lupus erythematosus. *Br J Rheumatol* 1996;35:248-54.
100. Alarcon GS, Roseman JM, McGwin G, Jr., Uribe A, Bastian HM, Fessler BJ et al. Systemic lupus erythematosus in three ethnic groups. XX. Damage as a predictor of further damage. *Rheumatology (Oxford)* 2004;43:202-5.
101. Levey AS, Coresh J, Greene T, Stevens LA, Zhang YL, Hendriksen S et al. Using standardized serum creatinine values in the modification of diet in renal disease study equation for estimating glomerular filtration rate. *Ann Intern Med* 2006;145:247-54.
102. Nakou ES, Liberopoulos EN, Milionis HJ, Elisaf MS. The role of C-reactive protein in atherosclerotic cardiovascular disease: an overview. *Curr Vasc Pharmacol* 2008;6:258-70.
103. Sutton EJ, Davidson JE, Bruce IN. The systemic lupus international collaborating clinics (SLICC) damage index: a systematic literature review. *Semin Arthritis Rheum* 2013;43:352-61.
104. Amara U, Flierl MA, Rittirsch D, Klos A, Chen H, Acker B et al. Molecular intercommunication between the complement and coagulation systems. *J Immunol* 2010;185:5628-36.
105. Shikata K, Makino H, Morioka S, Kashitani T, Hirata K, Ota Z et al. Distribution of extracellular matrix receptors in various forms of glomerulonephritis. *Am J Kidney Dis* 1995;25:680-8.
106. Podack ER, Kolb WP, Muller-Eberhard HJ. The C5b-6 complex: formation, isolation, and inhibition of its activity by lipoprotein and the S-protein of human serum. *J Immunol* 1978;120:1841-8.
107. Blasi F, Sidenius N. Efferocytosis: another function of uPAR. *Blood* 2009;114:752-3.
108. D'Mello V, Singh S, Wu Y, Birge RB. The urokinase plasminogen activator receptor promotes efferocytosis of apoptotic cells. *J Biol Chem* 2009;284:17030-8.
109. Park YJ, Liu G, Tsuruta Y, Lorne E, Abraham E. Participation of the urokinase receptor in neutrophil efferocytosis. *Blood* 2009;114:860-70.

110. Yang A, Dai J, Xie Z, Colman RW, Wu Q, Birge RB et al. High molecular weight kininogen binds phosphatidylserine and opsonizes urokinase plasminogen activator receptor-mediated efferocytosis. *J Immunol* 2014;192:4398-408.
111. Vandivier RW, Henson PM, Douglas IS. Burying the dead: the impact of failed apoptotic cell removal (efferocytosis) on chronic inflammatory lung disease. *Chest* 2006;129:1673-82.
112. Bae HB, Tadie JM, Jiang S, Park DW, Bell CP, Thompson LC et al. Vitronectin inhibits efferocytosis through interactions with apoptotic cells as well as with macrophages. *J Immunol* 2013;190:2273-81.
113. Rosenwald M, Koppe U, Keppeler H, Sauer G, Hennel R, Ernst A et al. Serum-derived plasminogen is activated by apoptotic cells and promotes their phagocytic clearance. *J Immunol* 2012;189:5722-8.
114. Park YJ, Liu G, Lorne EF, Zhao X, Wang J, Tsuruta Y et al. PAI-1 inhibits neutrophil efferocytosis. *Proc Natl Acad Sci U S A* 2008;105:11784-9.
115. Yang Y, Friggeri A, Banerjee S, Bdeir K, Cines DB, Liu G et al. Urokinase-type plasminogen activator inhibits efferocytosis of neutrophils. *Am J Respir Crit Care Med* 2010;182:1516-23.
116. Clancy RM, Neufing PJ, Zheng P, O'Mahony M, Nimmerjahn F, Gordon TP et al. Impaired clearance of apoptotic cardiocytes is linked to anti-SSA/Ro and -SSB/La antibodies in the pathogenesis of congenital heart block. *J Clin Invest* 2006;116:2413-22.
117. Briassouli P, Komissarova EV, Clancy RM, Buyon JP. Role of the urokinase plasminogen activator receptor in mediating impaired efferocytosis of anti-SSA/Ro-bound apoptotic cardiocytes: Implications in the pathogenesis of congenital heart block. *Circ Res* 2010;107:374-87.
118. Briassouli P, Rifkin D, Clancy RM, Buyon JP. Binding of anti-SSA antibodies to apoptotic fetal cardiocytes stimulates urokinase plasminogen activator (uPA)/uPA receptor-dependent activation of TGF-beta and potentiates fibrosis. *J Immunol* 2011;187:5392-401.
119. Briassouli P, Halushka MK, Reed JH, Molad Y, Fox-Talbot K, Buyon L et al. A central role of plasmin in cardiac injury initiated by fetal exposure to maternal anti-Ro autoantibodies. *Rheumatology (Oxford)* 2013;52:1448-53.
120. Kaplan MJ. Neutrophils in the pathogenesis and manifestations of SLE. *Nat Rev Rheumatol* 2011;7:691-9.
121. Knight JS, Kaplan MJ. Lupus neutrophils: 'NET' gain in understanding lupus pathogenesis. *Curr Opin Rheumatol* 2012;24:441-50.
122. Villanueva E, Yalavarthi S, Berthier CC, Hodgins JB, Khandpur R, Lin AM et al. Netting neutrophils induce endothelial damage, infiltrate tissues, and expose immunostimulatory molecules in systemic lupus erythematosus. *J Immunol* 2011;187:538-52.

123. Hakkim A, Furnrohr BG, Amann K, Laube B, Abed UA, Brinkmann V et al. Impairment of neutrophil extracellular trap degradation is associated with lupus nephritis. *Proc Natl Acad Sci U S A* 2010;107:9813-8.
124. Leffler J, Martin M, Gullstrand B, Tyden H, Lood C, Truedsson L et al. Neutrophil extracellular traps that are not degraded in systemic lupus erythematosus activate complement exacerbating the disease. *J Immunol* 2012;188:3522-31.
125. Bengtsson AA, Pettersson A, Wichert S, Gullstrand B, Hansson M, Hellmark T et al. Low production of reactive oxygen species in granulocytes is associated with organ damage in systemic lupus erythematosus. *Arthritis Res Ther* 2014;16:R120.
126. Gargiulo L, Longanesi-Cattani I, Bifulco K, Franco P, Raiola R, Campiglia P et al. Cross-talk between fMLP and vitronectin receptors triggered by urokinase receptor-derived SRSRY peptide. *J Biol Chem* 2005;280:25225-32.
127. Resnati M, Pallavicini I, Wang JM, Oppenheim J, Serhan CN, Romano M et al. The fibrinolytic receptor for urokinase activates the G protein-coupled chemotactic receptor FPRL1/LXA4R. *Proc Natl Acad Sci U S A* 2002;99:1359-64.
128. Sitrin RG, Pan PM, Blackwood RA, Huang J, Petty HR. Cutting edge: evidence for a signaling partnership between urokinase receptors (CD87) and L-selectin (CD62L) in human polymorphonuclear neutrophils. *J Immunol* 2001;166:4822-5.
129. Pliyev BK, Arefieva TI, Menshikov MY. Urokinase receptor (uPAR) regulates complement receptor 3 (CR3)-mediated neutrophil phagocytosis. *Biochem Biophys Res Commun* 2010;397:277-82.
130. Zhou MJ, Brown EJ. CR3 (Mac-1, alpha M beta 2, CD11b/CD18) and Fc gamma RIII cooperate in generation of a neutrophil respiratory burst: requirement for Fc gamma RIII and tyrosine phosphorylation. *J Cell Biol* 1994;125:1407-16.
131. Lateef A, Petri M. Unmet medical needs in systemic lupus erythematosus. *Arthritis Res Ther* 2012;14 Suppl 4:S4.

Figure legends

Figure 1. Surface-bound and soluble fragments of the urokinase plasminogen activator receptor

(uPAR). uPAR is composed of three domains (D) and a glycosyl phosphatidylinositol anchor which is attached to the cell surface. Enzymatic cleavage of uPAR and soluble uPAR (suPAR) results in different fragments with known and unknown functions. MMP = matrix metalloproteinase, uPA = urokinase plasminogen activator.

Figure 2. The association between the soluble urokinase plasminogen activator receptor (suPAR) and

organ damage increase. Serum suPAR was measured at study inclusion (2008-2011) and the SLICC/ACR Damage Index (SDI) increase was calculated by subtracting the SDI at study inclusion from the SDI value of 2013 (resulting in an interval of 2-5 years). Kruskal-Wallis with Dunn's post hoc test was used to assess statistical differences between groups. Crosses indicate the percentage of deceased patients for each SDI category.

Figure 3. Possible interactions of uPAR and suPAR in the pathogenesis of SLE.

The SLE pathogenesis implicates defects in the handling of apoptotic cells which causes inflammation, complement deficiency, immune complex deposition and organ damage. Organ damage can also be caused by medication side-effects. Serum suPAR levels mirror organ damage in SLE, but uPAR/suPAR (illustrated in the figure by three green domains) could possibly take active part in the pathogenesis by its regulation of efferocytosis, antigen expression and complement proteins.