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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; IFNα, 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 (IFNα) 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 IFNα-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 (D₁, D₂ and D₃) of which D₃ 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 D₁ 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 D₂ and D₃ domains [3]. Vitronectin, which is an extracellular matrix (ECM) protein [32], can bridge uPAR with β3 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) -1β 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 D₁ and D₃ units of uPAR and at the GPI-anchor, rendering three possible soluble forms (full length D₁-D₃, D₁D₃ and D₁, respectively) as well as two membrane-bound variants (full length and D₁D₃) (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\textsubscript{III} form of suPAR has an approximate molecular weight range of 40-45 kDa and the D\textsubscript{i} domain weight is around 16 kDa [50]. The biological functions of the different suPAR forms have not been fully revealed. D\textsubscript{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\textsubscript{iD\textsubscript{III}} fragment has distinct chemotactic properties due to a SRSRY motif in the linker region between the D\textsubscript{i} and D\textsubscript{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, is 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 β3 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 \textit{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 \textit{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 Colleague 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 \textit{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 \textit{et al.} did not adjust for age and sex [95], factors that are known to influence suPAR levels [7]. However, Qin \textit{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 ($p = 0.005, \text{standardized } \beta = 0.20$) 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≥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 DIII 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 FcyRIII (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


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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.
uPAR

Monocytes, neutrophils, endothelial cells, etc.

suPAR DI

suPAR D_{1D_{III}}

Binds uPA and vitronectin

Chemotactic

uPA, MMPs, elastase, plasmin, cathepsin G

Phospholipases, plasmin, cathepsin G

Monocytes, neutrophils, endothelial cells, etc.

Phospholipases, plasmin, cathepsin G
• Late apoptotic cells
• Necrotic cells
• Neutrophil NETosis

Autoantigen exposure

Immune complex formation

Mortality

Inefficient efferocytosis

Permanent organ damage

Inflammation

Tissue deposition

Complement deficiency

Medication

Side effects

Immune complex formation