suPAR, A Cardiovacular and Glomerular Biomarker

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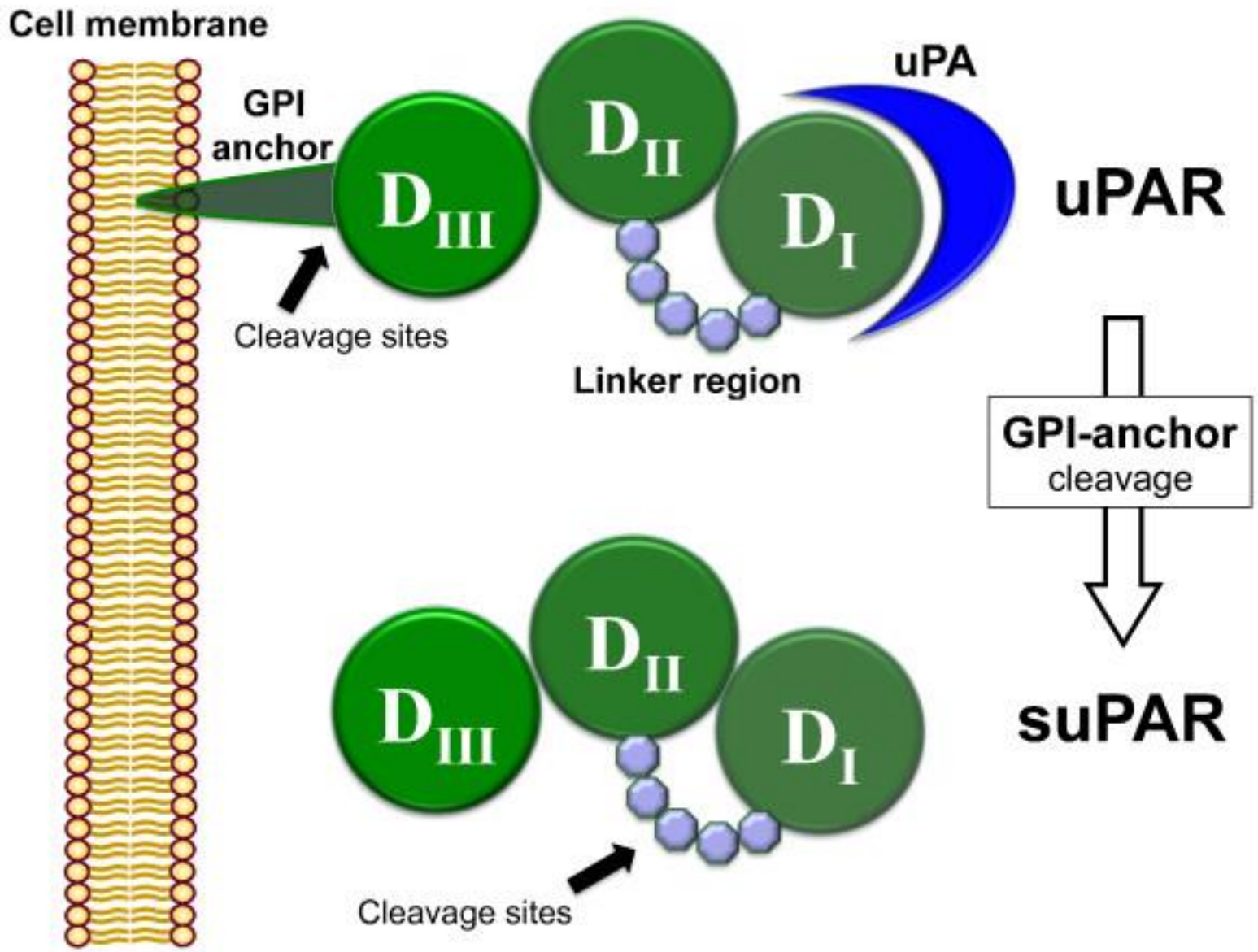
Introduction

- Urokinase plasminogen activator receptor (uPAR) is a multifaceted, (glyxosylphospatidylinositol) GPI-anchored three-domain protein as numbered from the N terminus.
- It acts as a receptor for urokinase-type plasminogen activator (uPA), facilitating the generation of activated plasmin, thus playing a role in the directional invasion of migrating cells.
- uPAR is a member of the lymphocyte antigen 6 (Ly-6) superfamily proteins.
- By cleavage of its GPI-anchor by cytokines such as TNF-α, uPAR can be released from the plasma membrane as soluble multi-domain signaling molecule (suPAR)
- suPAR is present under physiological conditions in low concentrations in human blood, and it has a known role as a circulating protein involved in neutrophil trafficking and stem cell mobilization.



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It can be elevated in some malignant neoplasms (for example, ovarian cancer) as well as in HIV infection.

Introduction

- Active uPA cleaves plasminogen to plasmin that activates matrix metalloproteases (MMPs degrade fibrin), cleaves extracellular matrix (ECM) components, and activates the complement pathway.
- uPA is also implicated in a plethora of cellular responses that include cell adhesion, cell migration, proliferation, differentiation, and cell survival in a non- proteolytic fashion as a signaling orchestrator.
- It can be elevated in some malignant neoplasms (for example, ovarian cancer) as well as in HIV infection.

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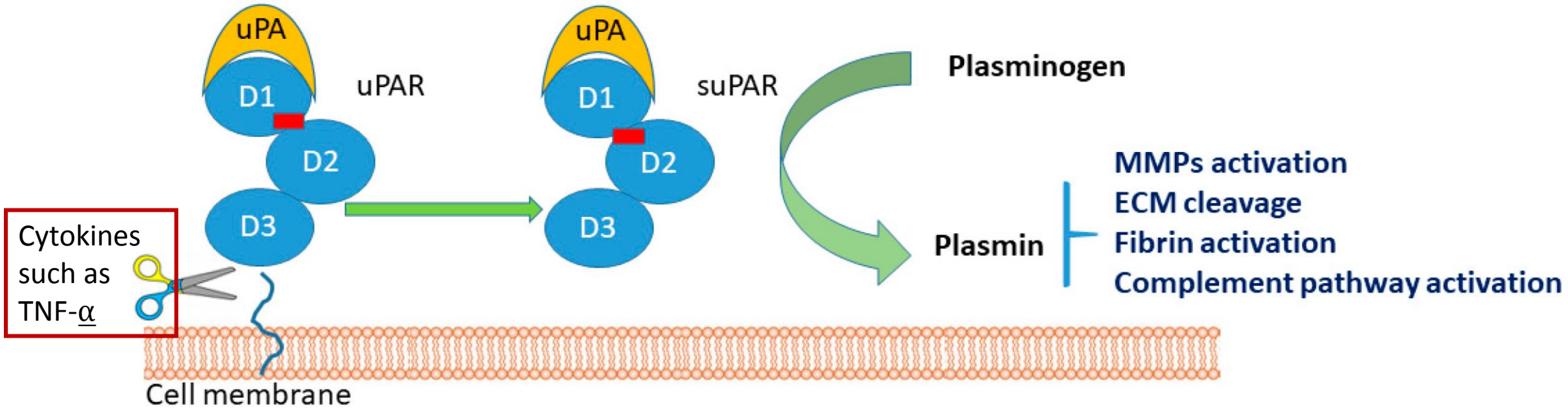
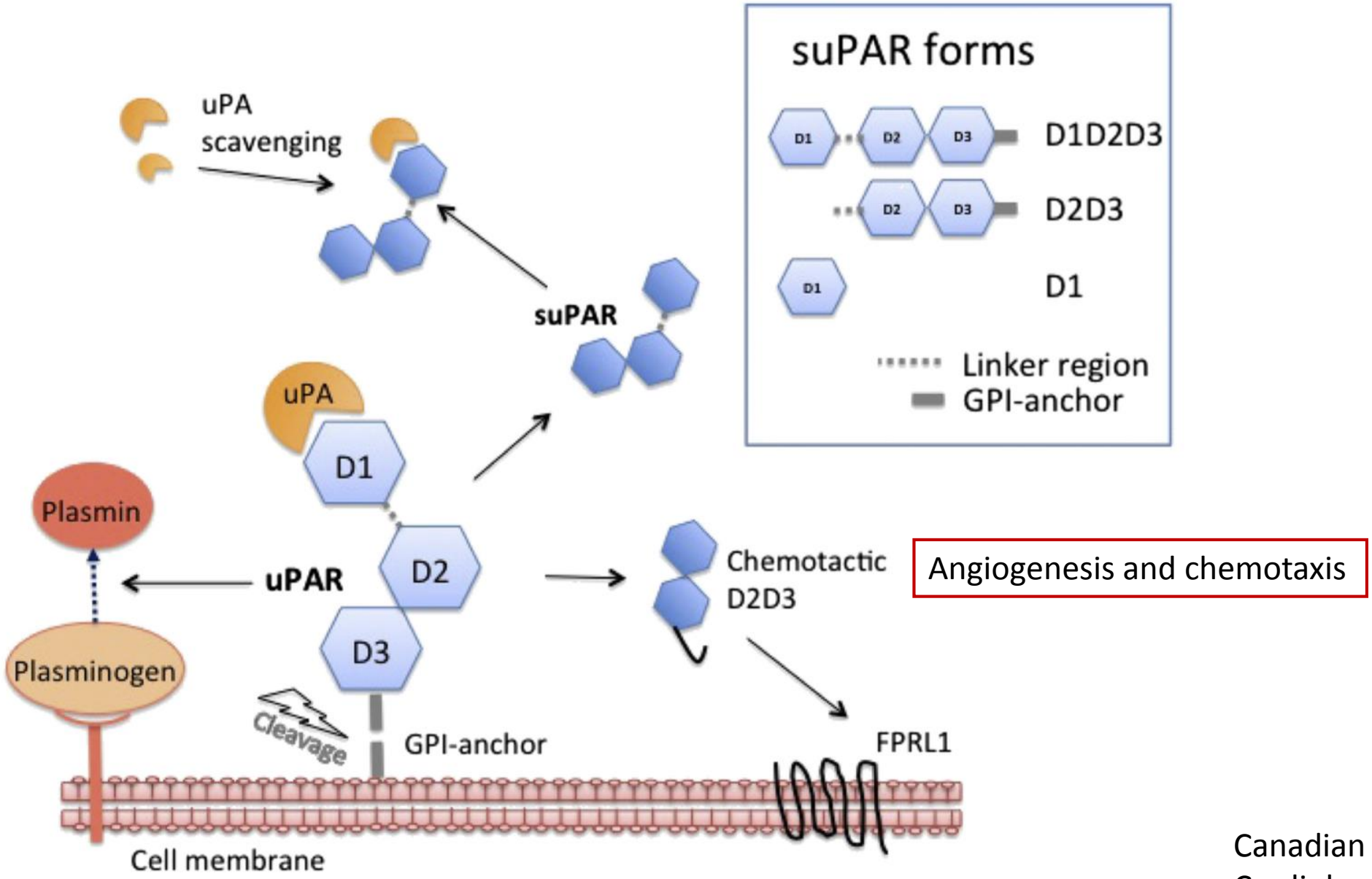




Angiogenesis and chemotaxis

Figure 1. suPAR is composed of 3 domains (D1-D3) and arises from cleavage of uPAR at the GPI-anchor. FPRL1, formyl peptide receptor-like-1; GPI, glycosylphosphatidylinositol; suPAR, soluble urokinase-type plasminogen activator receptor; uPAR, urokinase-type plasminogen activator.

Canadian Journal of Cardiology 2015

Introduction

- uPAR is expressed on a variety of cells, including monocyte, lymphocyte, endothelial cells.
- The efforts to examine the expression of uPAR in normal kidney and its alterations in kidney disease started in the mid 1990.
- Soluble urokinase plasminogen activated receptor (suPAR), a marker of podocyte injury, has been implicated in the pathogenesis of various kidney diseases.

suPAR and Kideny

- The investigators related the abnormal suPAR level to the pathogenesis of FSGS based on both in vitro and in vivo studies, which demonstrated suPAR binding to and, more importantly, activation of b3 integrin on podocytes.

suPAR and Kideny

- Induced uPAR expression in podocytes can cause podocyte foot process effacement and proteinuria, it is hypothesized that suPAR might be a candidate circulating factor in FSGS.
- Mechanistically, enhanced circulating suPAR deposits into the glomeruli, allowing activation of podocyte β3 integrin.
- This activation is sufficient to drive podocyte foot process effacement, proteinuria and initiation of FSGS.

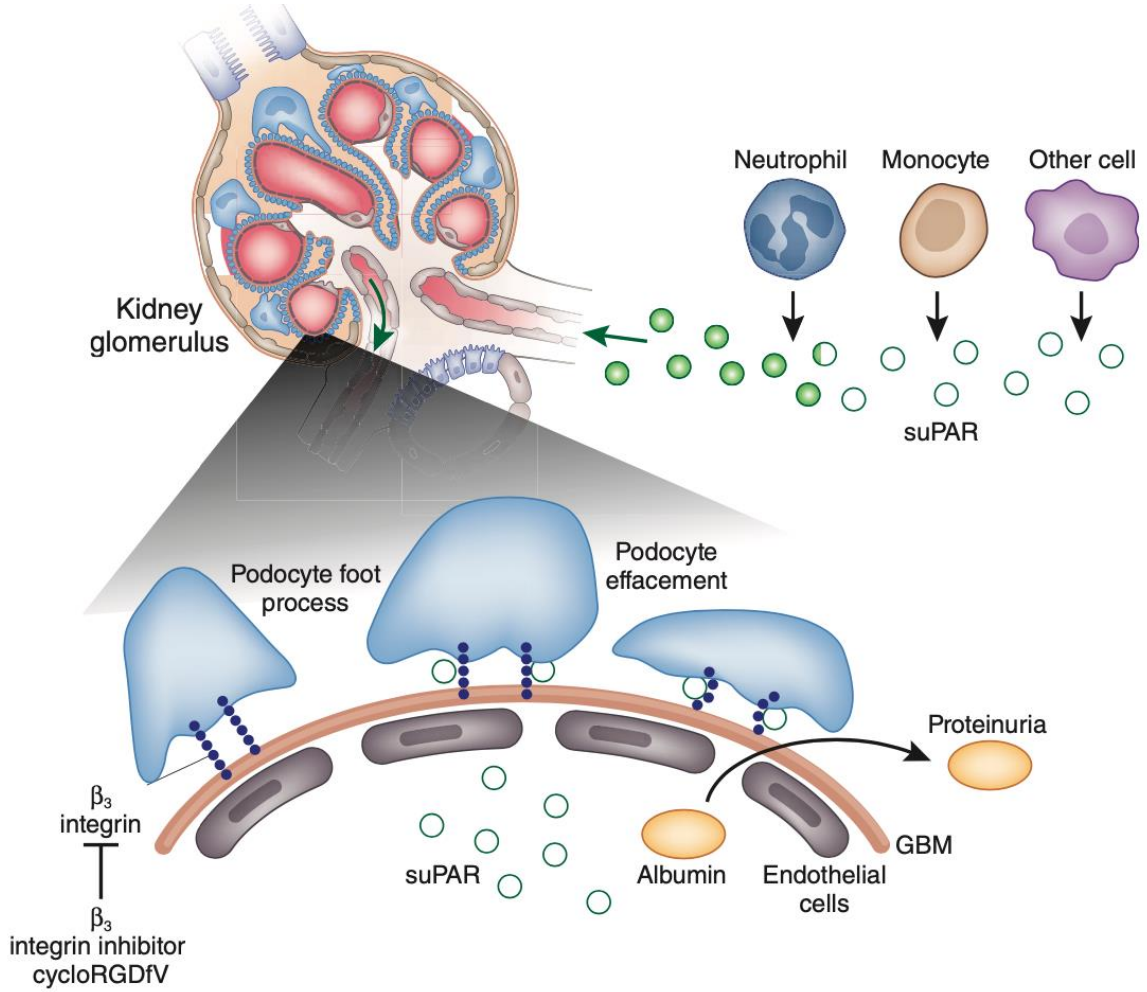


Figure 1 suPAR is a circulating factor that causes FSGS. Wei *et al.*[6] show that increased levels of the circulating permeability factor suPAR are found in the plasma of people with FSGS and provide mechanistic insights into how increased suPAR can lead to FSGS pathology. They suggest that suPAR is produced by neutrophils, monocytes and perhaps other cells, such as T cells, although the source of suPAR is still to be determined. suPAR enters the kidney glomerulus and binds and activates β_3 integrin, one of the major proteins anchoring podocytes to the underlying glomerular basement membrane (GBM). Increased plasma levels of suPAR lead to increased β_3 integrin activation, thus leading to podocyte dysfunction and effacement and proteinuria characteristic of FSGS.

®₃integrin is one of the main proteins
that anchors podocytes to the underlying glomerular basement membrane. suPAR-$\alpha v\beta 3$ integrin signaling is an important pathway in the pathogenesis of proteinuria in various kidney diseases.

August 2011 **nature medicine**

Focal and Segmental Glomerulosclerosis (FSGS)

- Represents up to 20 percent of glomerular disease and is a leading cause of end-stage kidney disease and is generally divided into two categories, primary and secondary
- Affects native kidneys as well as renal allografts
- Recurs after transplant in about 30% of adult and pediatric FSGS patients
- Considered to be a lesion with diverse clinical features and different pathophysiologic mechanisms and response to treatment

Focal and Segmental Glomerulosclerosis (FSGS)

- In its early stages targets mainly podocytes in kidney glomeruli
- Generally, the effacement of podocyte foot processes marks the first ultrastructural step associated with the loss of plasma proteins into the urine.
- Although podocyte gene defects are a known cause of human FSGS, there are cases in which FSGS occurs in the absence of gene defects or in which proteinuria recurs within a few hours or days after kidney transplantation.
- Circulating factors may be directly implicated in the pathogenesis of FSGS

The Role of Circulating Permeability Factors in FSGS

- A role of a circulating factor in the etiopathogenesis of FSGS has first been proposed in 1972, when Hoyer and colleagues described a case series of patients with recurrent FSGS after KT.
- Risk factors for disease recurrence include younger age, heavy proteinuria, higher baseline creatinine at the onset of the disease, and rapid progression to ESKD.
- Biopsies obtained from patients with recurrent FSGS resemble the same histologic subtype in a majority of patients.
- Plasmapheresis can remove the circulating factor and achieve remission in a subset of children and adults with FSGS

The Implication of suPAR In Proteinuric Kidney Disease

- The initial study of suPAR in proteinuric kidney disease was largely prompted by the concept of a circulating blood factor that causes primary or recurrent focal segmental glomerulosclerosis (FSGS).
- While many studies support the idea that primary FSGS is presumably caused by circulating permeability factors, the identification and characterizing of such factors have been challenging.

The Implication of suPAR in Proteinuric Kidney Disease

- suPAR fulfills the criteria of a circulating FSGS factor such as: elevated concentration in patients and the ability to signal to podocytes thereby causing injury and disease.
- However, there have also been controversies on this issue, because suPAR levels were also increased in those with other glomerular diseases and were inversely correlated with estimated glomerular filtration rate (GFR)
- Some other less characterized candidates for FSGS factor include active proteinases, cardiotrophin-like cytokine-1 (CLC-1), vasodilator-stimulated phosphoprotein (VASP), anti-CD40 antibodies and protein tyrosine phosphatase receptor O.

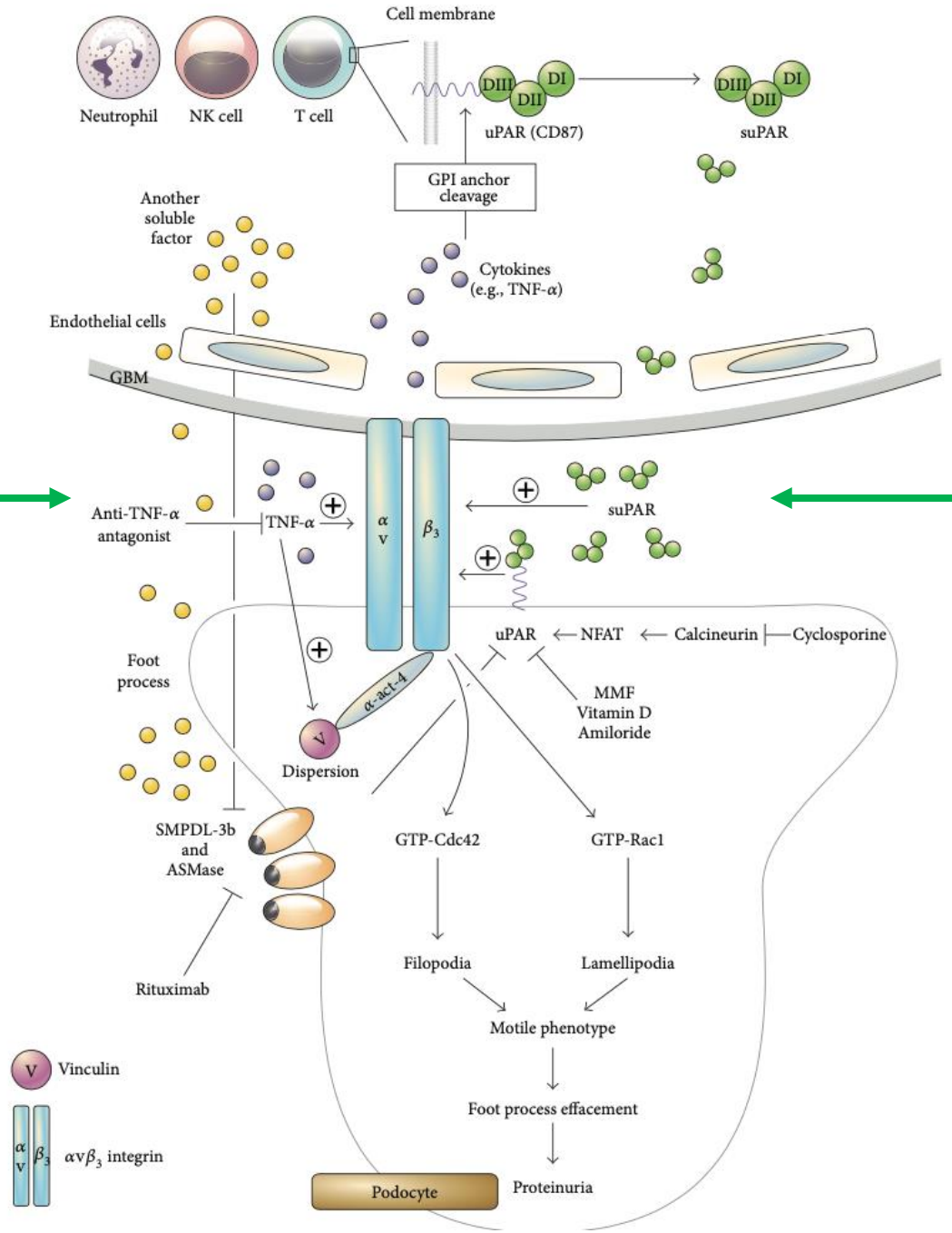
The Role of suPAR Signaling and Integrin Activation in Podocytes and Proteinuric Kidney Diseases

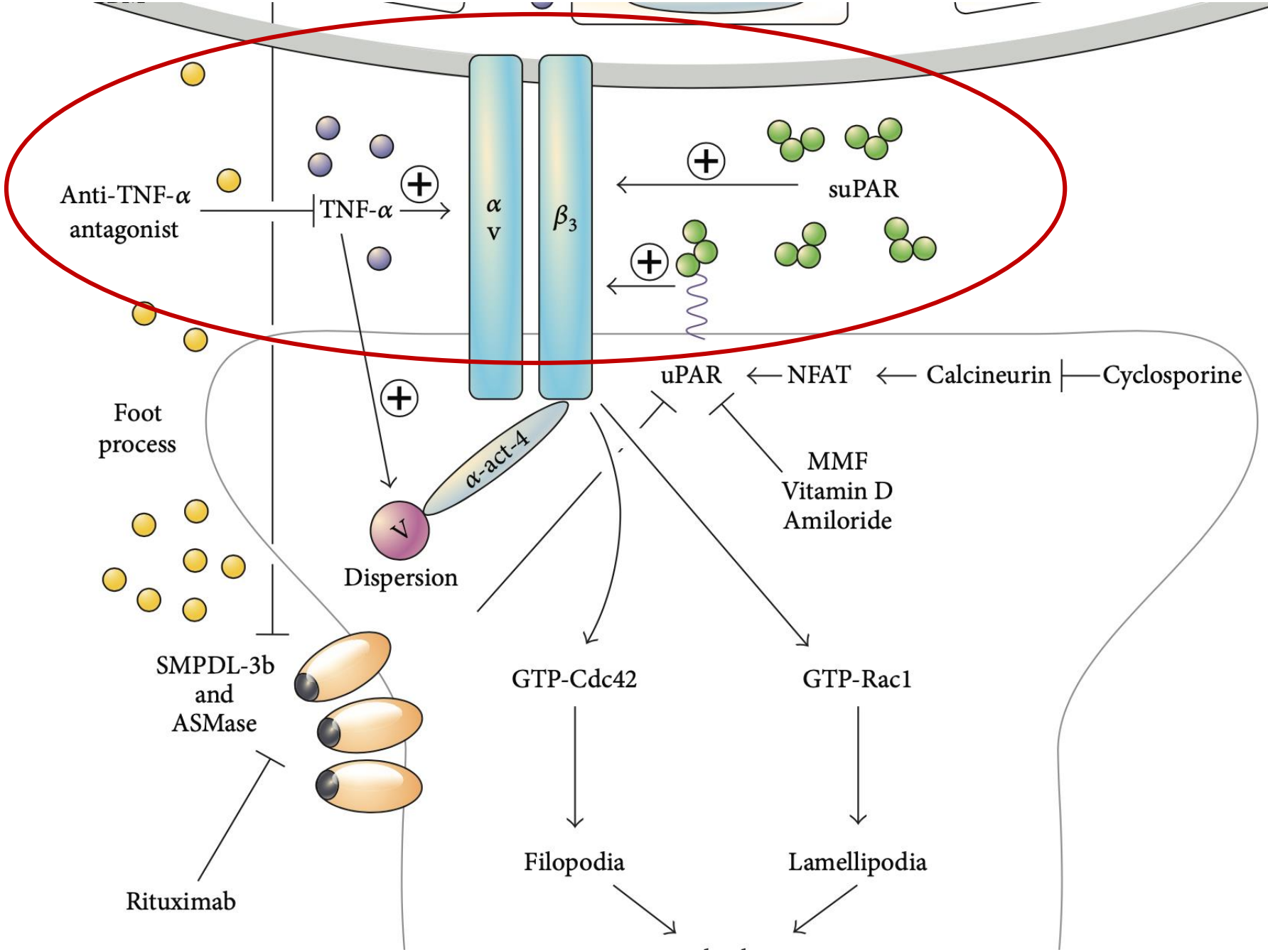
- Podocyte foot processes contain an actin cytoskeleton, which is connected to the glomerular basement membrane by $\alpha 3\beta 1$ and $\alpha v\beta 3$ integrin as well as α and β-dystroglycans.
- Induction of suPAR signaling in podocytes leads to foot process effacement and urinary protein loss by lipid-dependent activation of $\alpha v\beta 3$ integrin.
- Conversely, suPAR-induced glomerular disease can be blocked by expression of a suPAR point mutant that is strongly reduced in $\alpha v\beta 3$ integrin binding, or by use of neutralizing suPAR antibodies.

A hypothesis for the pathogenesis of suPAR-mediated FSGS

TNF-α can directly activate podocyte $\alpha v\beta_3$ integrin and vinculin

suPAR can activate $\alpha v\beta_3$ integrin of podocytes




Anti-TNF-α
antagonist
TNF-α
α
v
β3
suPAR
uPAR
NFAT
Calcineurin
Cyclosporine
Foot
process
α-act-4
V
Dispersion
MMF
Vitamin D
Amiloride
SMPDL-3b
and
ASMase
Rituximab
GTP-Cdc42
GTP-Rac1
Filopodia
Lamellipodia

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Circulating urokinase receptor as a cause of focal segmental glomerulosclerosis

Our findings suggest that the renal disease only develops when suPAR sufficiently activates podocyte β3 integrin. Thus, the disease can be abrogated by lowering serum suPAR concentrations through plasmapheresis, or by interfering with the suPAR–β3 integrin interaction through antibodies and small molecules targeting either uPAR or β3 integrin.

Our study identifies serum suPAR as a circulating factor that may cause FSGS.

Nature Med 2014

Subsequent Clinical Observations Supporting the Pathogenic Role of suPAR in FSGS

JUSTIFICATIONS

- the known possibility of massive proteinuria recurring within a few hours or even minutes of a renal transplantation in patients with primary FSGS
- the disappearance of this proteinuria whenever kidneys with proteinuria recurrence are retransplanted into a patient without FSGS
- induction of proteinuria in rats in which patient serum with primary FSGS is injected
- An infant with transient proteinuria born to a mother with FSGS revealed highly elevated suPAR levels in both the mother and the newborn
- the efficacy of plasmapheresis in cases of proteinuria recurrence in transplanted kidneys

Nat Med. 2011 Aug; 17(8): 952–960.

PMID: 21804539

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Circulating urokinase receptor as a cause of focal segmental glomerulosclerosis

Changli Wei,[1] Shafic El Hindi,[1,18] Jing Li,[1,18] Alessia Fornoni,[1,2,18] Nelson Goes,[3] Junichiro Sageshima,[4] Dony Maiguel,[1] S Ananth Karumanchi,[5] Hui-Kim Yap,[6] Moin Saleem,[7] Qingyin Zhang,[8] Boris Nikolic,[3] Abanti Chaudhuri,[9]

- uPAR activated $\beta 3$ integrin in a similar manner to membrane-bound uPAR in podocytes
- Podocyte $\beta 3$ integrin activation by suPAR was blocked by a blocking antibody specific to uPAR
- High-dose recombinant mouse suPARI–III induced podocyte integrin $\beta 3$ activation, proteinuria, and foot process effacement in a uPAR-knockout ($Plaur-/-$) mice
- suPAR is increased in FSGS compared to other glomerulopathies and healthy subjects

- suPAR is more increased in recurrent FSGS after KT than in nonrecurrent FSGS

- Pretransplant serum suPAR predicted recurrence of FSGS after KT Increasing serum suPAR levels after KT

Circulating suPAR in Two Cohorts of Primary FSGS

proven primary FSGS: 70 patients from the North America–based FSGS clinical trial (CT) and 94 patients from PodoNet, the Europe-based consortium studying steroid-resistant nephrotic syndrome. Circulating suPAR levels were elevated in 84.3% and 55.3% of patients with FSGS patients in the CT and PodoNet cohorts, respectively, compared with 6% of controls ($P<0.0001$); inflammation did not account for this difference. Multiple regression analysis suggested that lower suPAR levels associated with higher estimated GFR, male sex, and treatment with mycophenolate mofetil. In the CT cohort, there was a positive association between the relative reduction of suPAR after 26 weeks of treatment and reduction of proteinuria, with higher odds for complete remission ($P=0.04$). In the PodoNet cohort, patients with an *NPHS2* mutation had higher suPAR levels than those without a mutation. In conclusion, suPAR levels are elevated in geographically and ethnically diverse patients with FSGS and do not reflect a nonspecific proinflammatory milieu. The associations between a change in circulating suPAR with different therapeutic regimens and with remission support the role of suPAR in the pathogenesis of FSGS.

J Am Soc Nephrol 2012

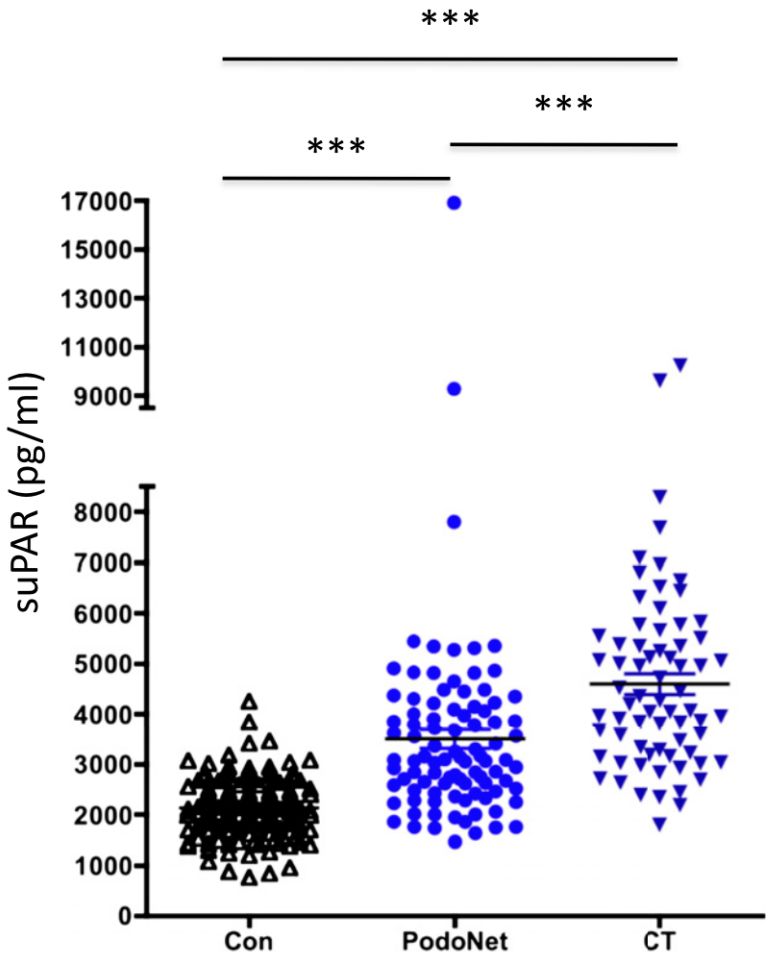


Figure 1. Serum suPAR levels in distinct primary FSGS cohorts and control participants. ***$P<0.001$ for CT FSGS cohort versus control, PodoNet FSGS cohort versus control, and CT versus PodoNet. Con, control.

Compared with control participants, the serum suPAR levels in FSGS patients were markedly increased in both FSGS cohorts

3000 pg/ml as a cut-off value was set based on the study dataset

The mean suPAR level was higher in the FSGS CT cohort than in the PodoNet cohort.

The mean serum creatinine was significantly higher in patients enrolled into the FSGS CT cohort than in PodoNet cohort, which might partially account for the difference of suPAR between the two groups

J Am Soc Nephrol 23: 2051–2059, 2012

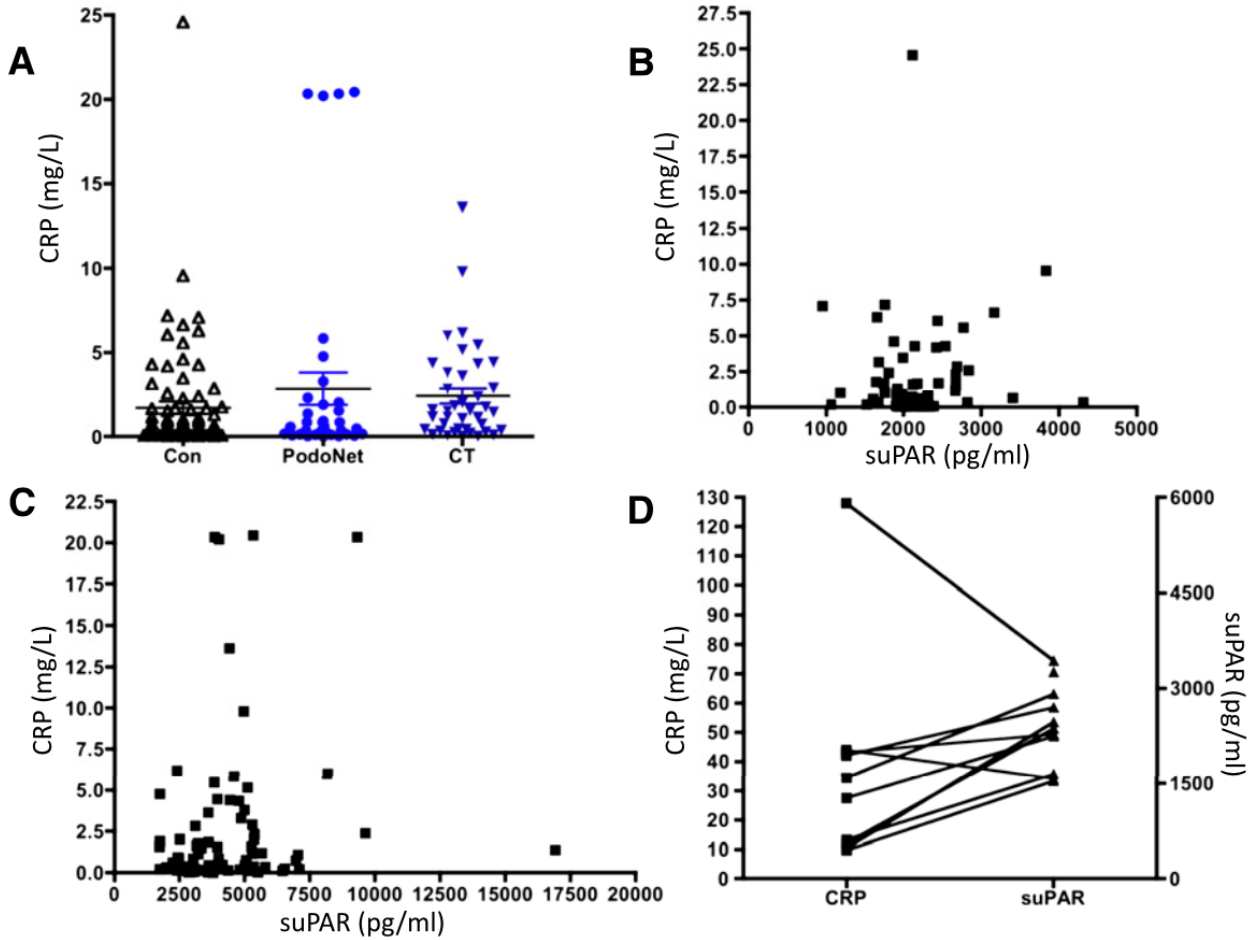


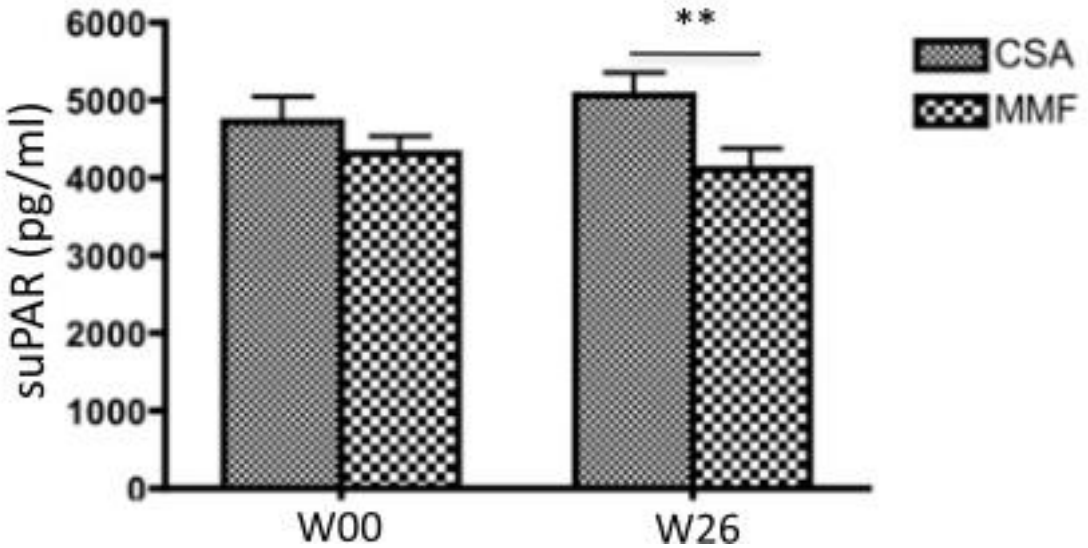
Figure 2. Serum CRP and its respective suPAR in FSGS patients and controls. (A) Serum CRP levels in FSGS patients. Control and FSGS patients from CT and PodoNet were determined for serum CRP concentration. Mean CRP was at low risk for inflammation and there was no difference between FSGS patients and controls. (B) Serum CRP did not correlate to its respective serum suPAR level in controls. (C) Serum CRP did not correlate to its respective suPAR in FSGS patients. (D) Patients with mild infection had high serum CRP level but presented with low suPAR concentration (*n*=11). Con, control.

In most cases in which suPAR is proposed as a marker of inflammation, CRP and suPAR are positively correlated with each other.

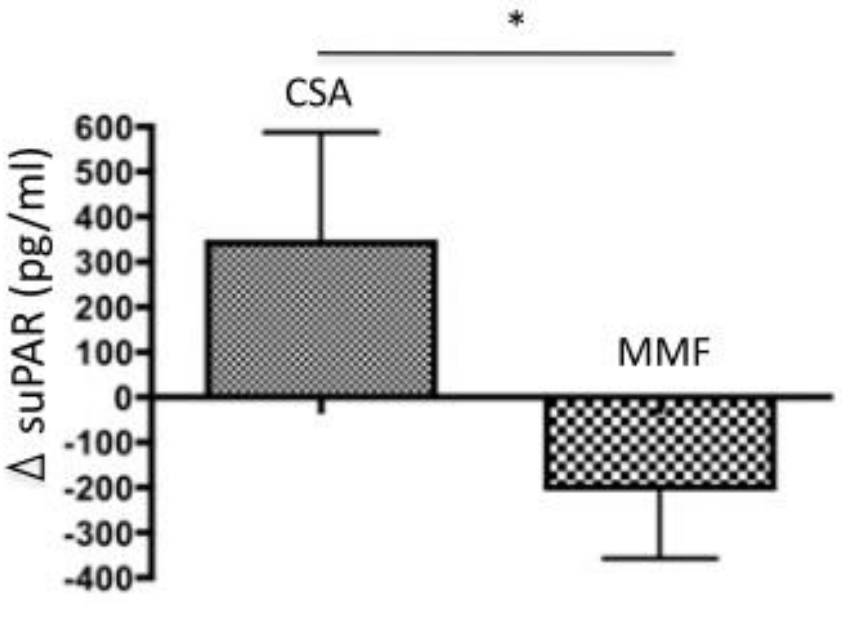
The average CRP levels were generally low, indicating minimal inflammation, and there was no difference between controls and FSGS patients.

This is consistent with the classification of FSGS as a noninflammatory renal disease.

J Am Soc Nephrol 23: 2051–2059, 2012

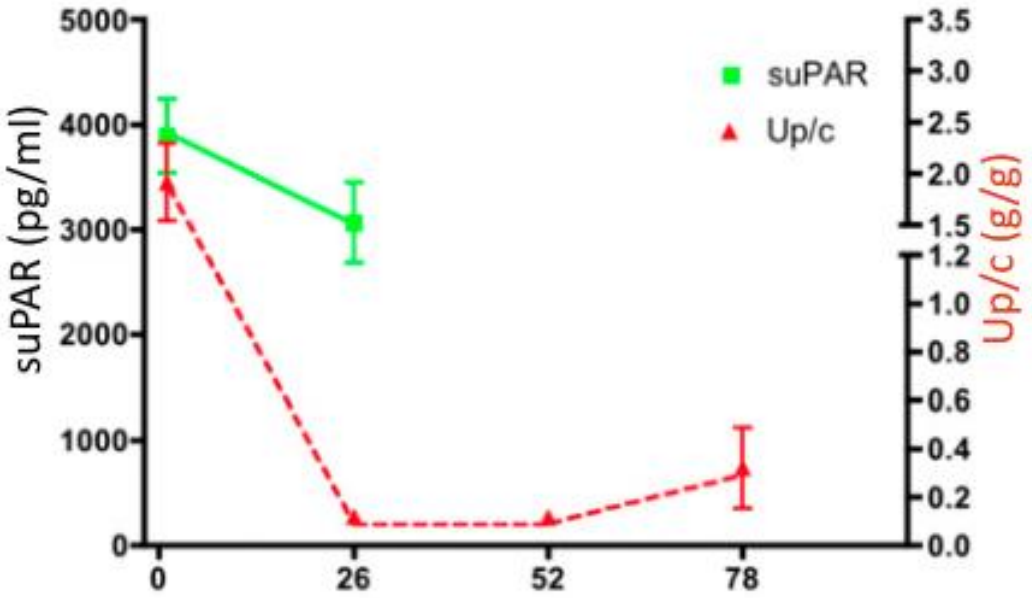


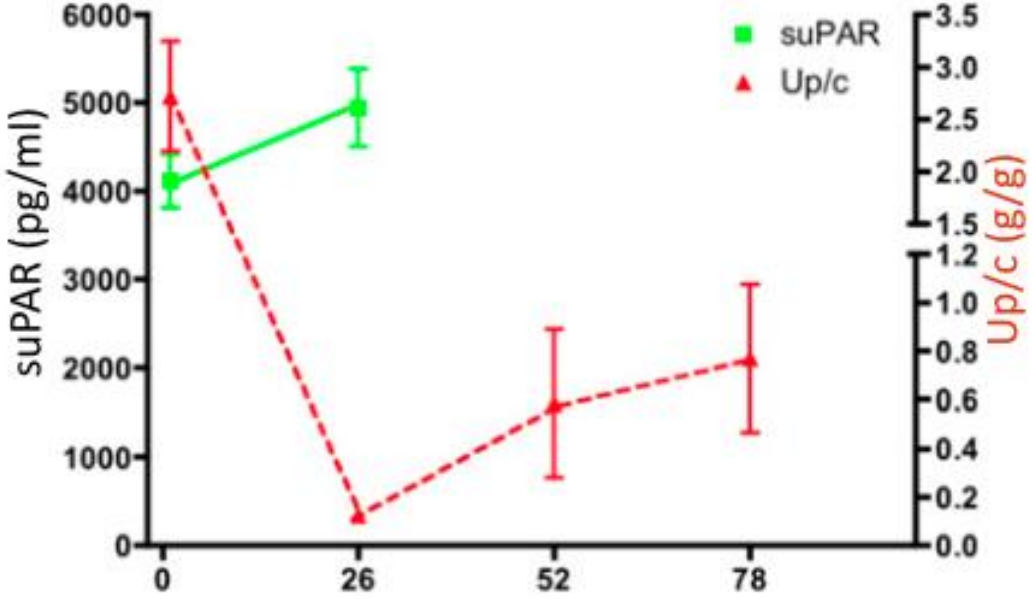
Circulating suPAR levels at baseline and 26 weeks after treatment



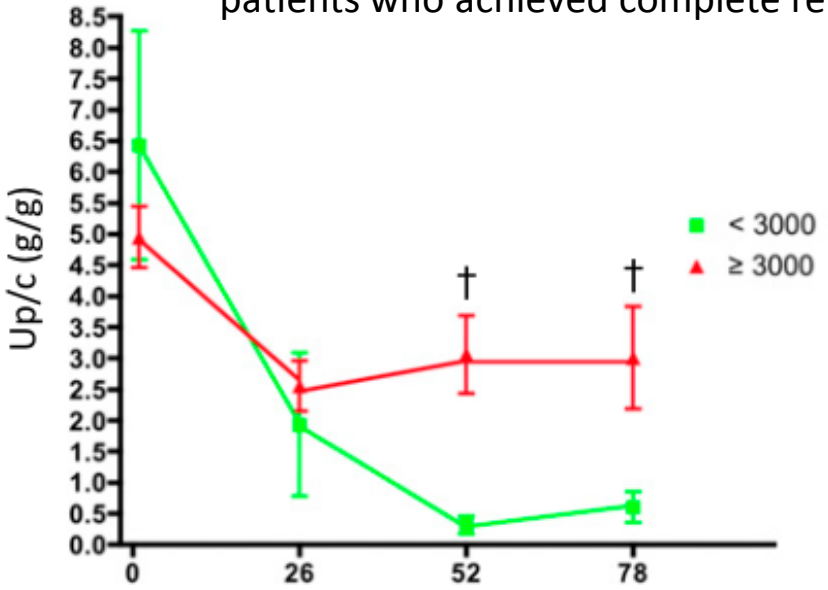
Therapy-associated changes of suPAR levels

J Am Soc Nephrol 23: 2051–2059, 2012



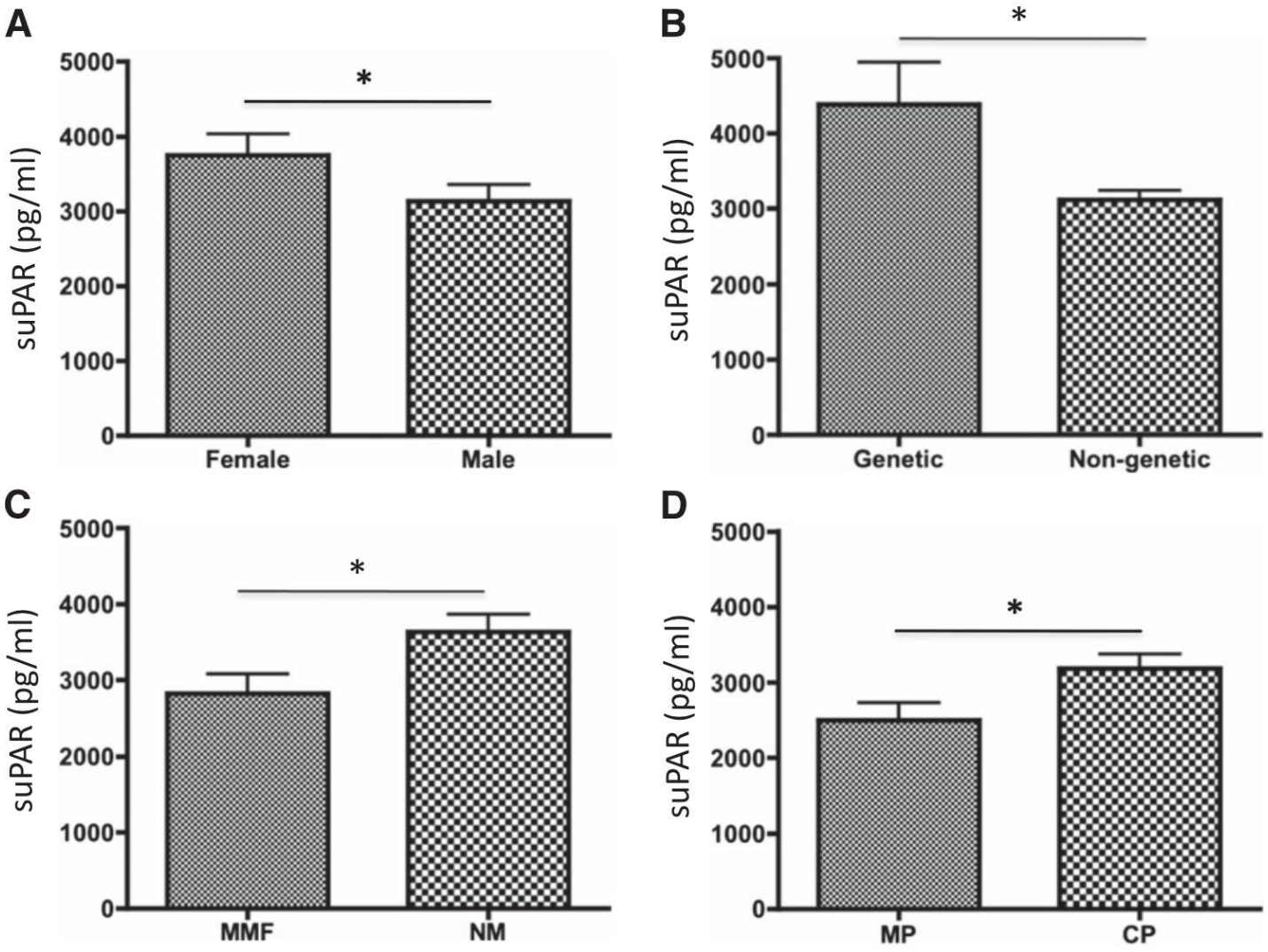


suPAR levels in patients who achieved complete remission at 26 weeks, and stabilized for at least 6 months vs patients who achieved complete remission at 26 weeks, but proteinuria came back at 52 weeks



suPAR responders were associated with a substantial decrease in Up/c. Responders were FSGS patients with high suPAR at baseline, but dropped to ,3000 pg/ml after 26-week therapy, whereas nonresponders were patients whose suPAR levels remained high

J Am Soc Nephrol 23: 2051–2059, 2012



Female FSGS patients had higher levels of suPAR compared with male FSGS patients. (B) Familial FSGS patients and/or FSGS patients who had NHPS2 mutation were associated with higher suPAR levels as indicated by univariate analysis. (C) MMF treatment was associated with lower suPAR levels. (D) Patients received MMF plus prednisone possessed lower suPAR levels compared with those received calcineurin inhibitor and prednisone

J Am Soc Nephrol 23: 2051–2059, 2012

Justification

- Case reports emerged showing that lowering circulating suPAR levels through plasmapheresis or immunoadsorption could reduce proteinuria in recurrent FSGS, making it an effective therapy for some transplant FSGS patients
- Conversely, transmission of elevated suPAR from a mother with FSGS to her child was correlated to the child being born with proteinuria
- Bone marrow (BM)-derived immature myeloid cells (IMCs) are likely a main source of circulating suPAR, thereby contributing to proteinuric kidney diseases.

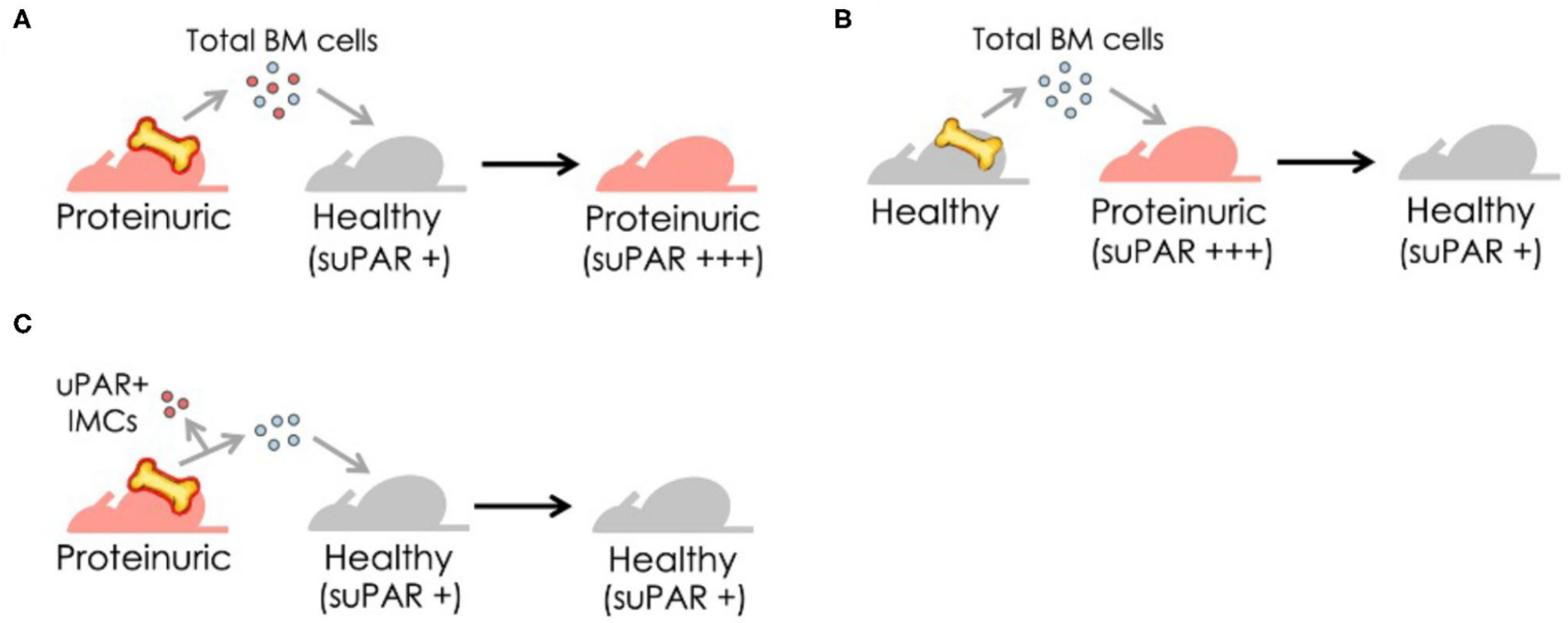


FIGURE 1 | Bone marrow (BM)-derived immature myeloid cells (IMCs), newly identified as a cellular source of suPAR, transfer disease from proteinuric to healthy mice. **(A)** Transfer of BM cells from proteinuric to healthy mice results in proteinuria and increases blood suPAR levels. **(B)** Replacement with BM cells from healthy mice significantly reduces suPAR levels and subsequently improves renal function in proteinuric mice. **(C)** The removal of uPAR-expressing IMCs prior to transfer of BM cells from proteinuric to healthy mice protects mice from proteinuria.

Areas of Uncertainty concerning the Sources of suPAR

- Various suPAR fragments exist with different characteristics and whether or not the “true” circulatory factor is a cleaved suPAR isoform remains obscure.
- In addition, it should be considered that a glycosylation status of suPAR may be causative of inducing proteinuria in primary FSGS.
- Therefore, isoforms and glycosylation status of suPAR should be considered and detection kits should be developed in the future.

suPAR/uPAR, More Than Just One Look

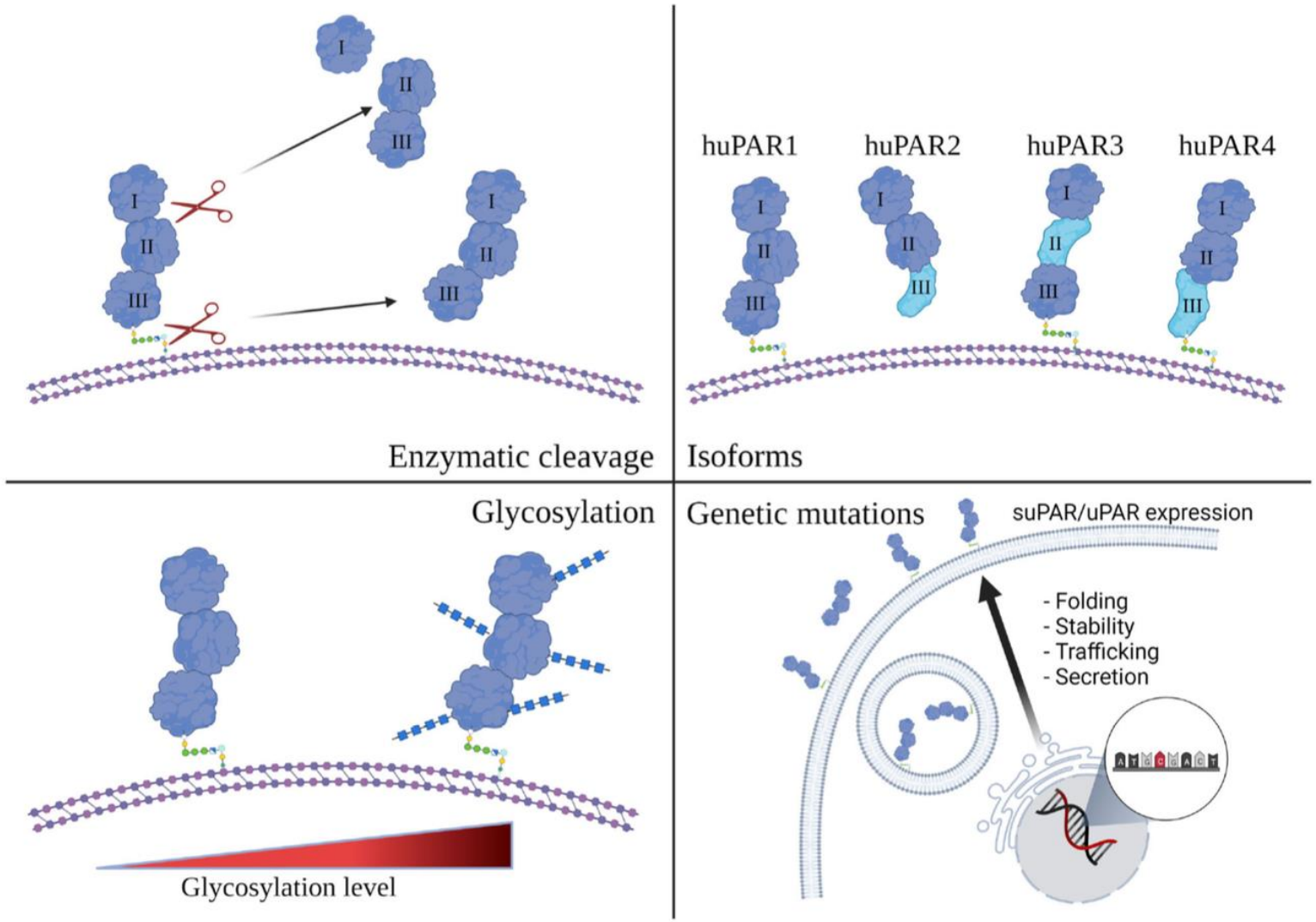


FIGURE 2 | Human suPAR, more than just one flavor. Schematic presentation of human uPAR and suPAR (Created with BioRender.com). While enzymatic cleavage has been considered to be the main source of suPAR, transcriptional splicing, genetic mutation, and post-translational glycosylation could also impact the composition and function of circulating suPAR in different human subjects.

While enzymatic cleavage has been considered to be the main source of suPAR, transcriptional splicing, genetic mutation, and post-translational glycosylation could also impact the composition and function of circulating suPAR in different human subjects.

Frontiers in Medicine, October 2021

Major uPAR isoforms in mouse and human.

	Isoform	Exon	Domains	GPI anchor	Length (Amino acid)	Nucleotide ID	Protein ID
Mouse	Isoform 1 canonical form, muPAR1	7 Exons (1–7)	Three intact domains (I, II, III)	Yes	327	NM_011113	NP_035243
	Isoform 2 secreted, muPAR2	Exons 5 to 7 missing	DIII and part of DII missing	No	222	BC010309	CAA44575
Human	Isoform 1 canonical form, huPAR1	7 Exons (1–7)	Three intact domains (I, II, III)	Yes	335	NM_002659	NP_002650
	Isoform 2 secreted, huPAR2	Exon 7 missing	C-terminal part of DIII missing	No	281	NM_001005376	NP_001005376
	Isoform 3, huPAR3	Exon 5 missing	Part of DII missing	Likely	290	NM_001005377	NP_001005377
	Isoform 4, huPAR4	Exon 6 missing	N-terminal part of DIII missing	Likely	286	NM_001301037	NP_001287966

What is the implication of different human uPAR isoforms in kidney?

Among these human uPAR isoforms, huPAR3 seems to be the closest to muPAR2 at least structurally. It likely forms the same dimer assembly observed in the msuPAR (associated with FSGS-like kidney changes in mouse model) structure

Frontiers in Medicine, October 2021

Research Article

Kidney Diseases

Kidney Dis 2019;5:239–246
DOI: 10.1159/000497353

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Published online: May 27, 2019

Soluble Urokinase Receptor Levels in Secondary Focal Segmental Glomerulosclerosis

Methods: Fifty-two secondary FSGS patients diagnosed by kidney biopsy, including 8 with Alport-FSGS, 20 with obesity-related FSGS, and 24 with diabetic nephropathy, were enrolled in the study in the period from January 2008 to June 2014 at the Renal Division, Peking University First Hospital. Fifty-six healthy donors and 74 patients with primary FSGS, 14 with minimal-change disease, and 29 with membranous nephropathy were used as healthy controls and disease controls, respectively. Plasma and urinary suPAR concentrations were measured with commercial ELISA kits, and their correlations with clinical and pathological data were analyzed.

Conclusions: The levels of plasma and urinary suPAR in patients with Alport-FSGS, obesity-related FSGS, and diabetic nephropathy were increased.

Plasma suPAR might be a pathogenetic participation factor or a useful marker of glomerular diseases with FSGS-associated podocytopathy but is not necessarily a circulating permeability factor.

Areas of Uncertainty Concerning suPAR Serum Determinants

- suPAR levels increases after an observation time of 72 hours
- C-reactive protein (CRP) or erythrocyte sedimentation rate (ESR) should be determined, since inflammation per se can affect suPAR levels
- Accumulation of suPAR in patients at low GFR may obfuscate FSGS-induced suPAR accumulation
- Cut-off point 3.2 ng/mL, suPARnostic assay.

suPAR serum determinants (collection time of blood, ethnic differences, systemic inflammation, eGFR, and metabolism of suPAR) should be considered in interpreting the results.

Clinical Observations Not Supporting the Pathogenic Role of suPAR in FSGS

Although increased suPAR levels resulted in FSGS-like glomerular lesions and proteinuria in PLAUR−/− (uPAR-deficient mice), the pathogenic effects of suPAR were not observed in wild-type mice, in which proteinuria or podocyte foot process effacement did not occur despite glomerular suPAR deposition.

Pediatr Nephrol (2012) 27:2217–2226
DOI 10.1007/s00467-012-2163-3

ORIGINAL ARTICLE

TNFα pathway blockade ameliorates toxic effects of FSGS plasma on podocyte cytoskeleton and β3 integrin activation

Martin Bitzan · Sima Babayeva · Anil Vasudevan · Paul Goodyer · Elena Torban

We suggest that in some FSGS patients, disruption of the podocyte cytoskeleton and β3 integrin-mediated podocyte attachment are driven by the TNFα pathway

UPO UNIVERSITÀ DEL PIEMONTE ORIENTALE

Circulating suPAR levels are affected by glomerular filtration rate and proteinuria in primary and secondary glomerulonephritis

Claudio Musetti, Marco Quaglia, Tiziana Cena, Annalisa Chiocchetti, Sara Monti, Nausicaa Clemente, Corrado Magnani, Umberto Dianzani, Piero Stratta

This study shows that elevated serum suPAR levels are associated with reduced eGFR and presence of proteinuria in both primary and secondary GN, suggesting that circulating suPAR may represent a common biomarker of renal involvement in a wide spectrum of GN.

KEY POINTS

- Experimental studies have shown that suPAR, through activation of podocyte β3 integrins, causes massive pedicel fusion and nephrotic syndrome. These data, along with the fact that anti-uPAR antibodies have a clearly positive effect, resulted in suPAR being proposed as the potential circulating factor causing primary FSGS.
- Patients with FSGS have higher suPAR levels than those with other forms of glomerulonephritis, although there is a considerable overlap and not all studies agree. Age and reduction of renal function increase suPAR values.

KEY POINTS

- suPAR levels are high in various clinical conditions (sepsis, tumours, liver disease, lupus), which reduces its specificity. Very high levels of suPAR in these conditions are not associated with proteinuria, which calls into question its pathogenic role as a proteinuric circulating factor.
- suPAR levels above 3531pg/ml would support the diagnosis of FSGS versus minimal change disease in cases of dubious histologies. Levels greater than 4000pg/ml would support the diagnosis of primary glomerulosclerosis versus the secondary form.

suPAR: A New Biomarker for Cardiovascular Disease?

- Conventional risk factors have been shown to be moderately effective in predicting outcomes in patients with cardiovascular disease.
- However, up to 20% of patients who present with cardiovascular disease have no traditional risk factors.
- Cardiac biomarkers are used to predict or prognosticate the presence or severity of a cardiac condition, and have been proposed to supplement conventional risk factors.
- An ideal biomarker should be inexpensive, easy to measure, stable in plasma, serum, and blood samples, accurately differentiate patient outcomes, and help guide the treatment of a specific patient.

The most well known biomarkers include:

- high-sensitivity C-reactive protein (hs-CRP):a marker of inflammation
- Albuminuria: a marker of renal dysfunction
- Troponin: a marker of cardiac damage
- Brain natriuretic protein (BNP): a marker of volume overload
- Fibrinogen: a marker of the coagulation cascade

Even common biomarkers such as hs-CRP and endothelial function markers have not gained general acceptance because of cost issues, logistic concerns, or lack of studies that show effects on hard clinical end points.

suPAR as a cardiac biomarker

- suPAR has been linked to endothelium dysfunction, damaged cardiac microcirculation, increased vascular stiffness, and finally, more extensive atherosclerosis.
- Because it regulates fibrin as part of the coagulation system, it was later evaluated as a biomarker for an expanding list of diverse cardiovascular diseases, including stroke, myocardial infarction, heart failure, abdominal aortic aneurysms, coronary restenosis, and advanced atherosclerosis.

suPAR and Subclinical Organ Damage (SOD)

- Monitoring Trends and Determinants in Cardiovascular Disease **(MONICA) study** compared suPAR with CRP, measuring their relation with anthropometric measures (**BMI and waist circumference**) and SOD (**presence of atherosclerotic plaques and elevated UACR, the latter believed to be a marker of endothelial dysfunction, a crucial step in atherosclerosis**).
- After adjusting for age, sex, smoking, and physical activity, results showed that suPAR correlated more closely with endothelial dysfunction and atherosclerosis.

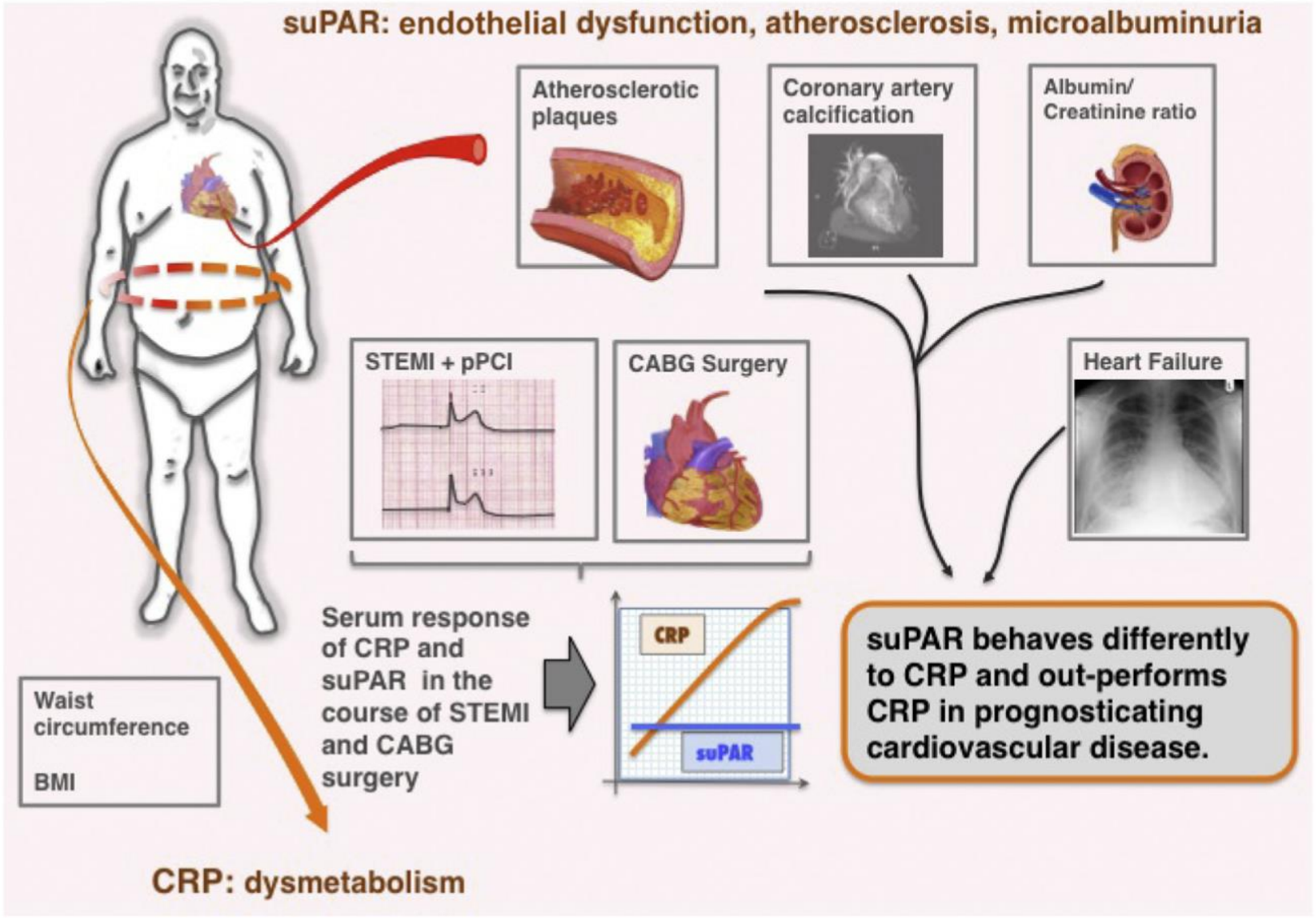


Figure 2. suPAR vs CRP. CRP is predominantly associated with dysmetabolism compared with suPAR, which is related to endothelial dysfunction, atherosclerotic plaques, coronary calcification, and microalbuminuria. BMI, body mass index; CABG, coronary artery bypass surgery; CRP, C-reactive protein; suPAR, soluble urokinase-type plasminogen activator receptor; STEMI, ST-elevation myocardial infarction.

In cardiology a cut-off value range of 3.5 - 4.5 ng/mL has been commonly utilized. Different cut-off values may be applied based on the measuring kit used, the patient population and the clinical setting.

Canadian Journal of Cardiology Volume 31 2015

Atherosclerotic plaques and suPAR

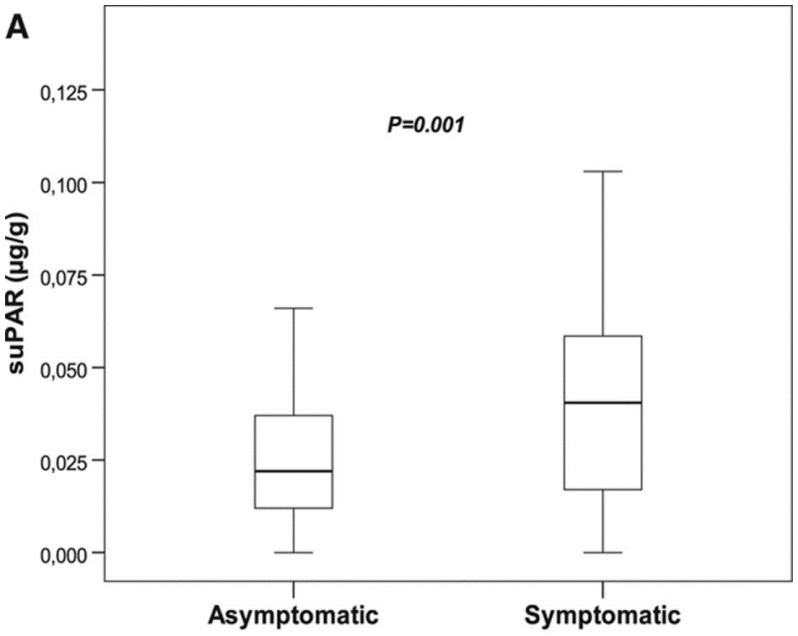
Soluble Urokinase Plasminogen Activator Receptor is Associated With Inflammation in the Vulnerable Human Atherosclerotic Plaque

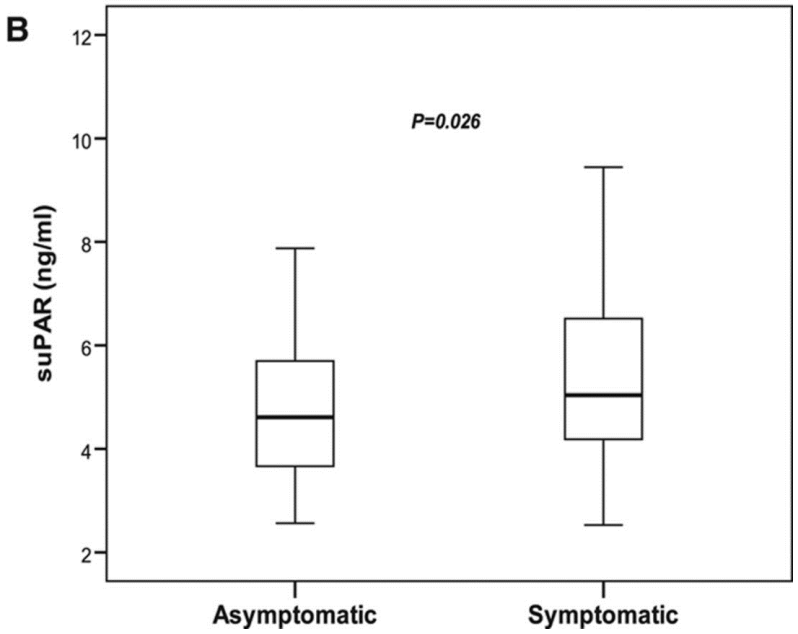
Andreas Edsfeldt ✉, Mihaela Nitulescu, Helena Grufman, Caitriona Grönberg, Ana Persson, Marie Nilsson, Margaretha Persson, Harry Björkbacka and Isabel Gonçalves

Conclusion

This study shows that suPAR in human carotid plaques and plasma is associated with the presence of symptoms and that plaque suPAR is associated with the vulnerable inflammatory plaque.

These findings strengthen the hypothesis of suPAR as a future marker of vulnerable atherosclerotic plaques.

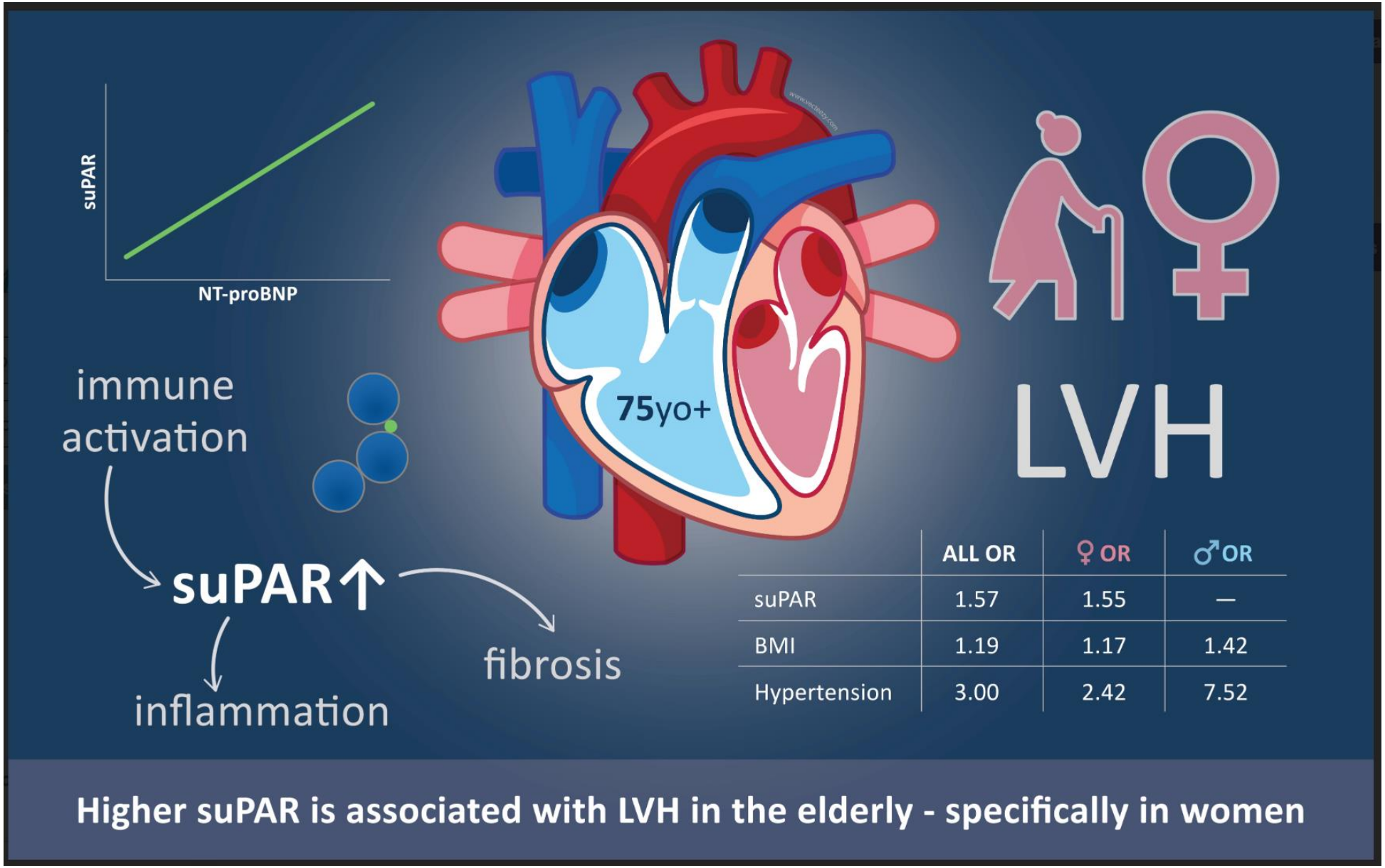




Stroke 2012

suPAR, CVD and NT-proBNP

- In the Danish MONICA cohort, Eugen-Olsen et al. demonstrated that elevated levels of suPAR were associated with the incidence of CVD, type 2 DM, cancer, and mortality.
- Several studies show that NT-proBNP is a strong predictor of adverse cardiovascular outcomes.
- In a study from Sweden, suPAR was significantly correlated with NT-proBNP and was further shown to predict heart failure after adjustment for traditional risk factors, including NT-proBNP.



	ALL OR	♀ OR	♂ OR
suPAR	1.57	1.55	—
BMI	1.19	1.17	1.42
Hypertension	3.00	2.42	7.52

suPAR level is an independent predictor of LVH, especially in women, and additionally that it is associated with worse LV diastolic function.

J. Clin. Med. **2023**

suPAR as a biomarker in AF and low EF

Contents lists available at ScienceDirect

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Original Article

Association between serum soluble urokinase-type plasminogen activator receptor and atrial fibrillation

Noboru Ichihara, Masatoshi Miyamura, Daichi Maeda, Tomohiro Fujisaka, Shu-ichi Fujita, Hideaki Morita, Yoshihiro Takeda, Takahide Ito, Koichi Sohmiya, Masaaki Hoshiga, Nobukazu Ishizaka*

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Serum suPAR was associated with AF, particularly NPAF. Whether suPAR promotes or maintains AF should be investigated in further studies.

PLOS ONE

OPEN ACCESS PEER-REVIEWED

RESEARCH ARTICLE

Serum Soluble Urokinase-Type Plasminogen Activator Receptor Is Associated with Low Left Ventricular Ejection Fraction and Elevated Plasma Brain-Type Natriuretic Peptide Level

suPAR was associated with low LVEF and elevated BNP, but not with left ventricular hypertrophy, independent of CRP, renal function, and diuretic use among cardiac inpatients who were not undergoing chronic hemodialysis.

Currently, there does not seem to be adequate clinical justification for measurement of suPAR levels in routine clinical practice

- First, in contrast to other biomarkers (eg, low-density lipoprotein, albuminuria, hs-CRP, BNP, troponin), the cutoff levels have not been sufficiently clinically validated.
- Second, there are significant gaps in our understanding of the factors that regulate suPAR levels. It is not clear why women have higher levels and why suPAR is not linked with obesity.
- Third, there are no currently recognized therapies to consistently decrease suPAR levels, and the clinical benefits of decreasing suPAR levels are not known.

conclusions

- suPAR is intimately related with the pathophysiology of cardiac diseases; but in the light of the requirement for a biomarker with acceptable diagnostic and prognostic specificity and sensitivity, further research is necessary before the integration of suPAR into daily clinical practice in cardiology.
- In the field of cardiovascular disease, suPAR is more promising as a prognostic indicator for improved accuracy in patient risk stratification than as a purely diagnostic biomarker.
- If it were to become routinely available to clinicians, it may be of value for the identification of patients at risk of adverse outcomes when used alongside other laboratory tests, imaging studies and clinical rating scales.
- It is however necessary to validate the reference range of suPAR in a variety of different settings in this field, and to determine appropriate cut-off values for risk stratification prior to advocating for widespread clinical use.