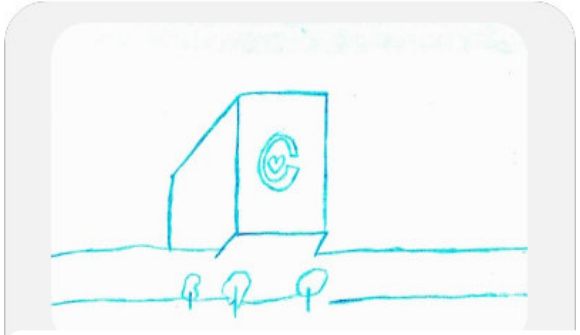


(suPAR) – klucz do FSGS ?

Ryszard Grenda

XII Konferencja

Polskiego Towarzystwa Nefrologii Dziecięcej
Lublin 2013

Autor nie ma konfliktu interesów związanego z tematem prezentacji

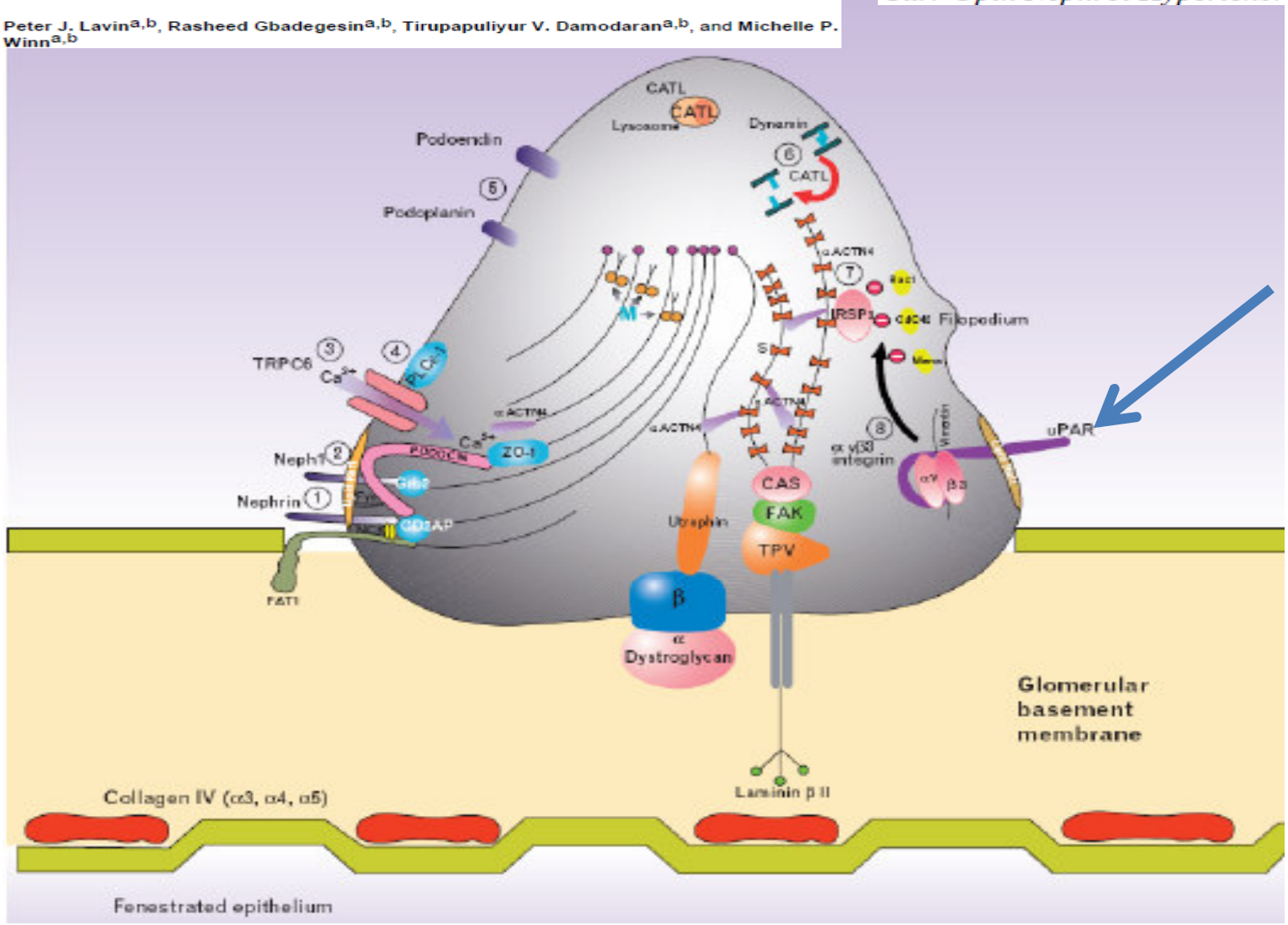

SUPAR ?....

http://supar.org

Therapeutic targets in focal and segmental glomerulosclerosis

Peter J. Lavin[a,b], Rasheed Gbadegesin[a,b], Tirupapuliyur V. Damodaran[a,b], and Michelle P. Winn[a,b]

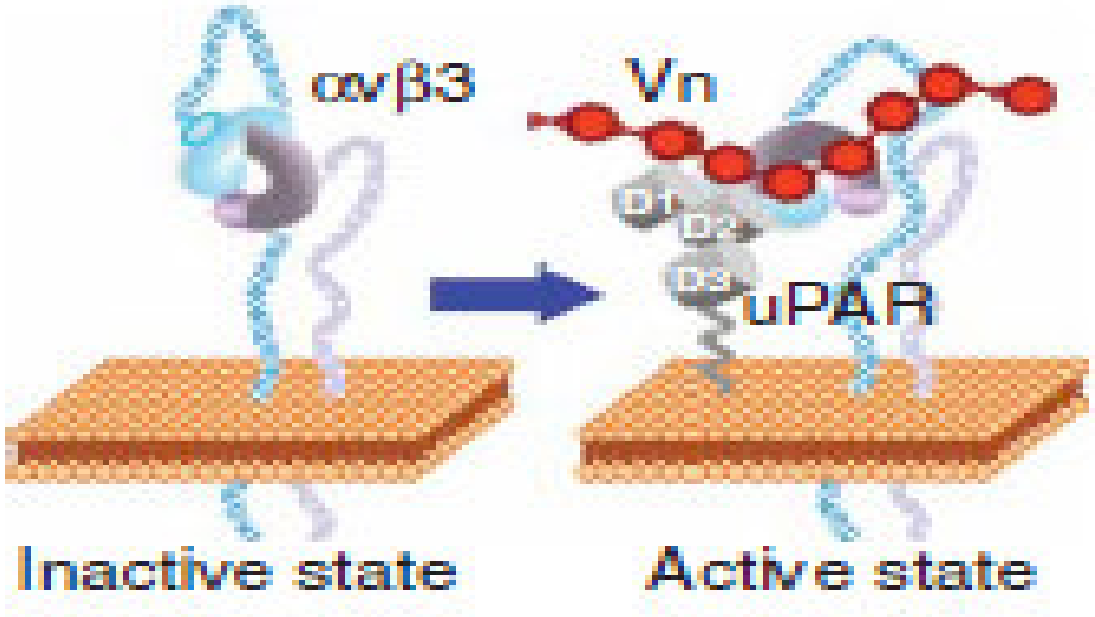
Curr Opin Nephrol Hypertens. 2008



Urokinase plasminogen activator receptor (uPAR) is a glycosylphosphatidylinositol (GPI) protein anchored to the lipid raft at the slit diaphragm.

Rozpuszczalny receptor urokinazowego aktywatora plazminogenu

uPAR-mediated podocyte motility and proteinuria involves αvβ3 integrin and vitronectin.



Wei *et al.* [14•] showed that induction of uPAR leads to foot process effacement and proteinuria through lipid dependent activation of αvβ3 integrin.

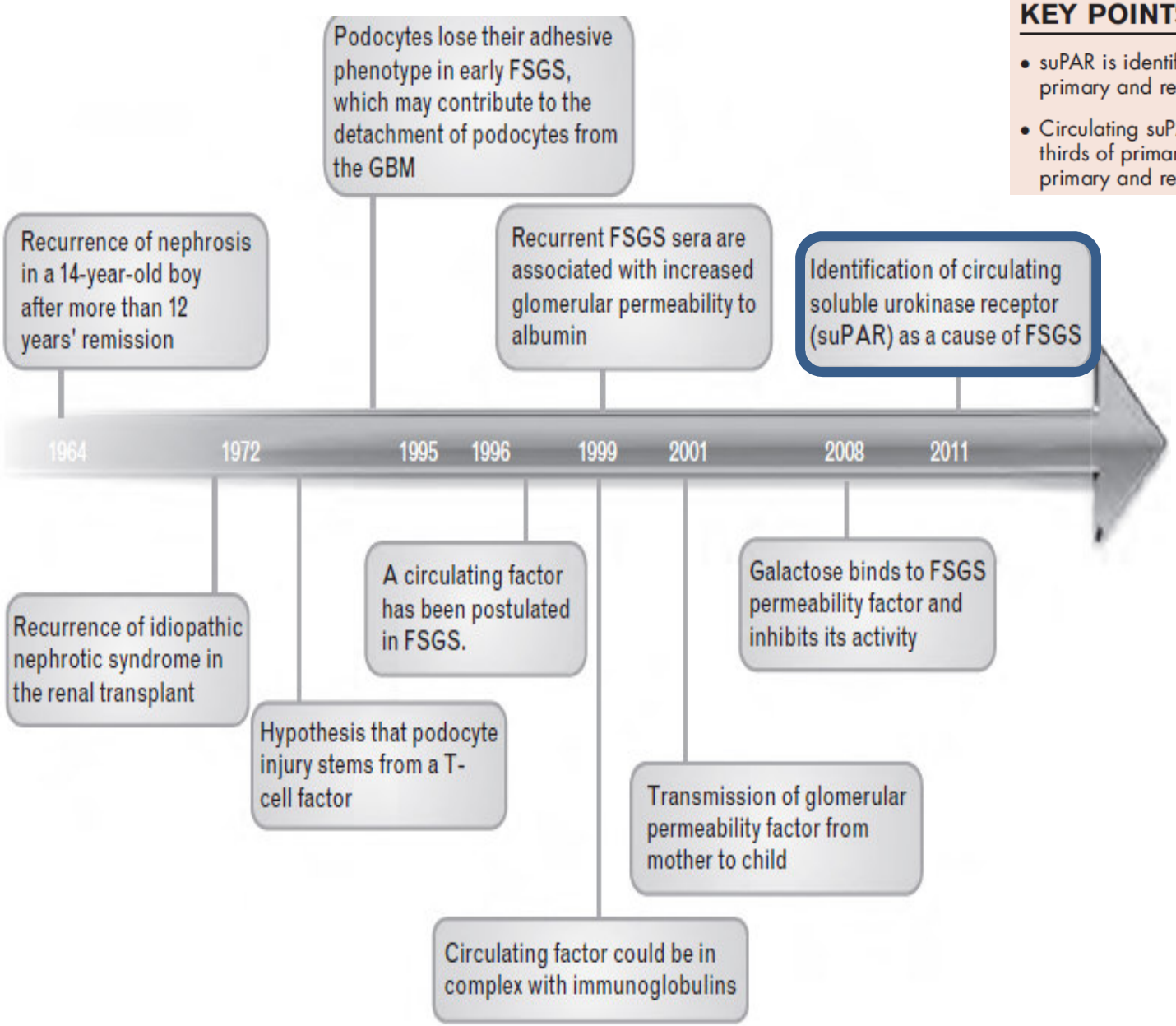
Soluble urokinase receptor and focal segmental glomerulosclerosis

Curr Opin Nephrol Hypertens 2012, 21:428–432

Jochen Reiser[a], *Changli Wei*[a], *and James Tumlin*[b]

KEY POINTS

- suPAR is identified as a circulating factor causing primary and recurrent FSGS.
- Circulating suPAR is elevated in approximately two-thirds of primary FSGS, and it confers risk to both primary and recurrent FSGS.



Circulating Permeability Factors in Idiopathic Nephrotic Syndrome and Focal Segmental Glomerulosclerosis

Clin J Am Soc Nephrol 5: 2115–2121, 2010

Ellen T. McCarthy,* Mukut Sharma,† and Virginia J. Savin†

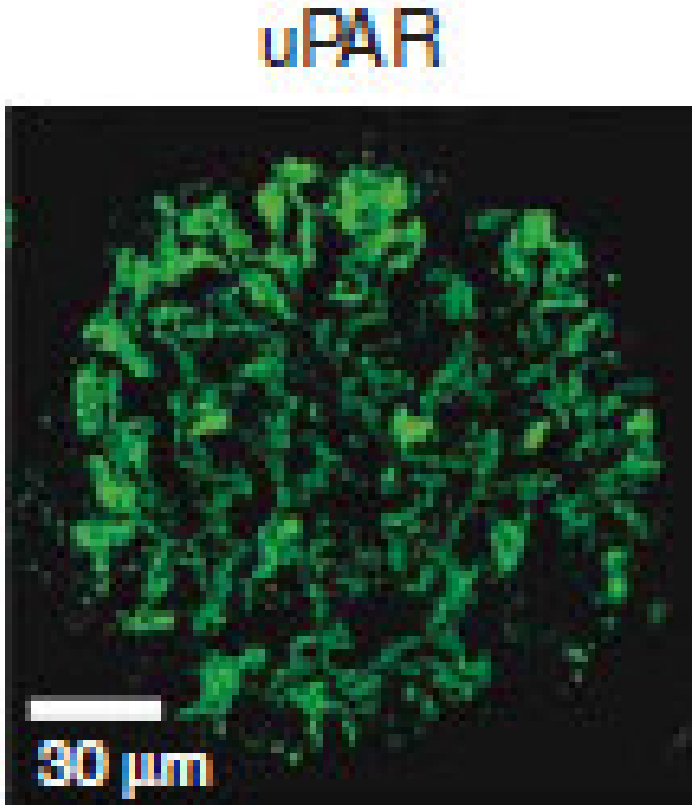
**Kidney Institute, University of Kansas Medical Center, Kansas City, Kansas; and †Kansas City VA Medical Center, Kansas City, Missouri*

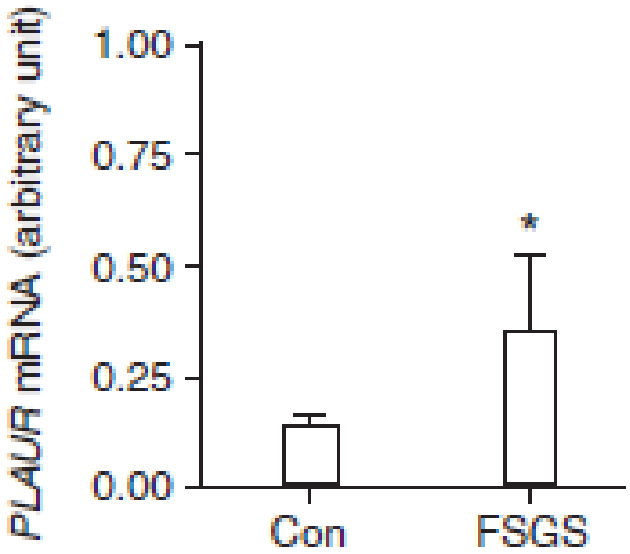
Evidence for circulating factor(s) in nephrotic syndrome caused by MCNS and FSGS

Clinical Observations/Identified Mediators	Experimental Findings
MCNS	
vascular permeability activity of serum of INS patients	Generation of permeability factor by T lymphocytes (VPF)
increased urinary protease, hemopexin, in active INS	Proteinuria after hemopexin injection into rats. Altered nephrin expression and glomerular endothelial cell monolayer permeability by hemopexin
FSGS	
immediate recurrence of proteinuria after transplantation; efficacy of plasmapheresis, immunoadsorption in reducing proteinuria	Induction of proteinuria in rat after injection of FSGS serum or plasma; increased glomerular permeability after incubation with plasma/ fraction
suPAR increased in FSGS plasma	suPAR activates uPAR
CLC-1 in active fraction of plasmapheresis fluid from recurrent FSGS patients	CLC-1 increases glomerular permeability, decreases nephrin expression, FSGS permeability activity blocked by anti-CLC-1

Modification of kidney barrier function by the urokinase receptor

Changli Wei[1], Clemens C Möller[1], Mehmet M Altintas[1], Jing Li[1], Karin Schwarz[2], Serena Zacchigna[3,4], Liang Xie[5], Anna Henger[6], Holger Schmid[7], Maria P Rastaldi[8], Peter Cowan[9], Matthias Kretzler[6], Roberto Parrilla[10], Moïse Bendayan[11], Vineet Gupta[1], Boris Nikolic[1], Raghu Kalluri[5], Peter Carmeliet[3,4], Peter Mundel[12] & Jochen Reiser[1]

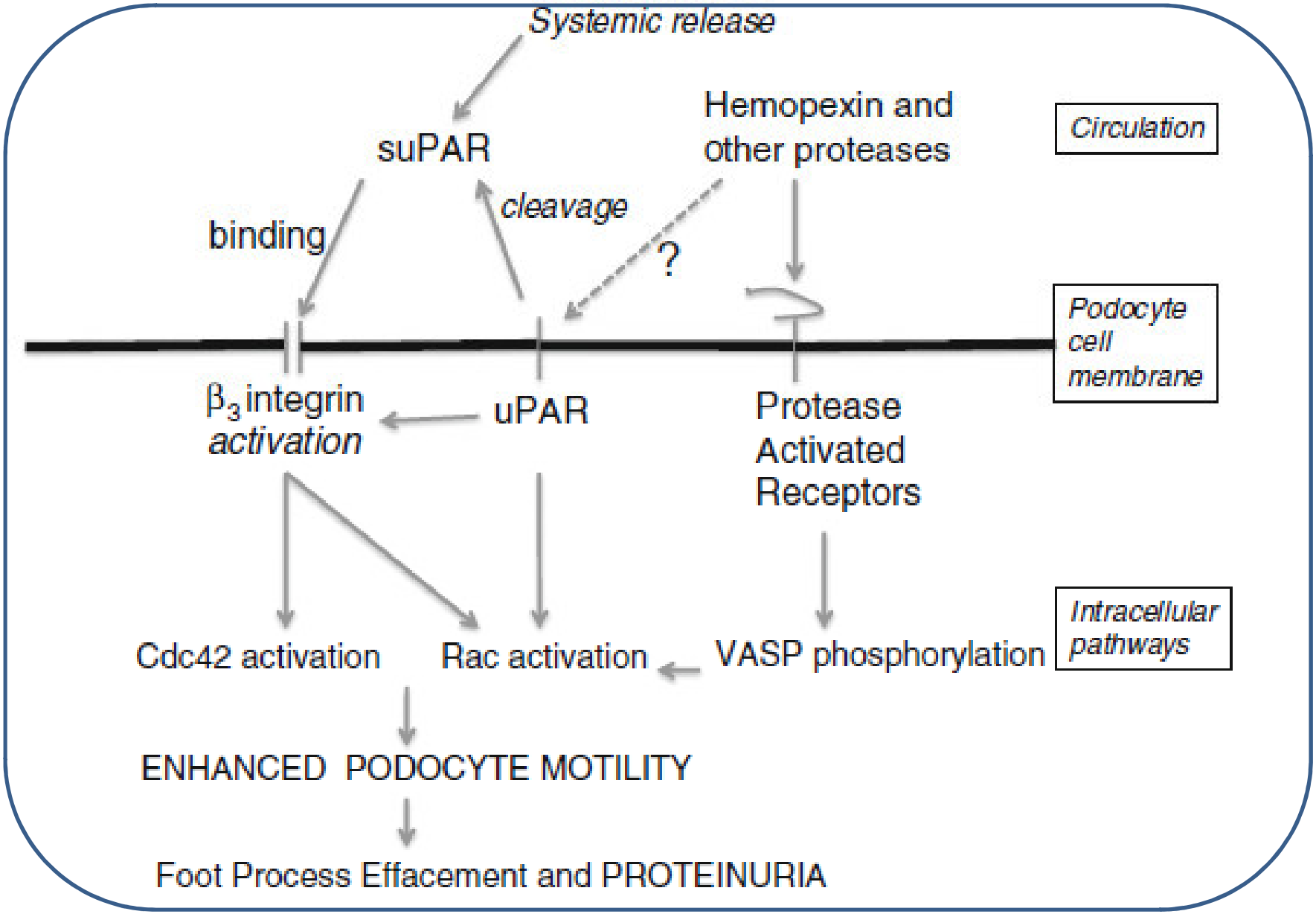




New developments in steroid-resistant nephrotic syndrome

Pediatr Nephrol

Moin A. Saleem



Soluble and cleaved forms of the urokinase-receptor: degradation products or active molecules?

Nunzia Montuori, Valeria Visconte, Guido Rossi, Pia Ragno

Thromb Haemost 2005: 93: 192-8

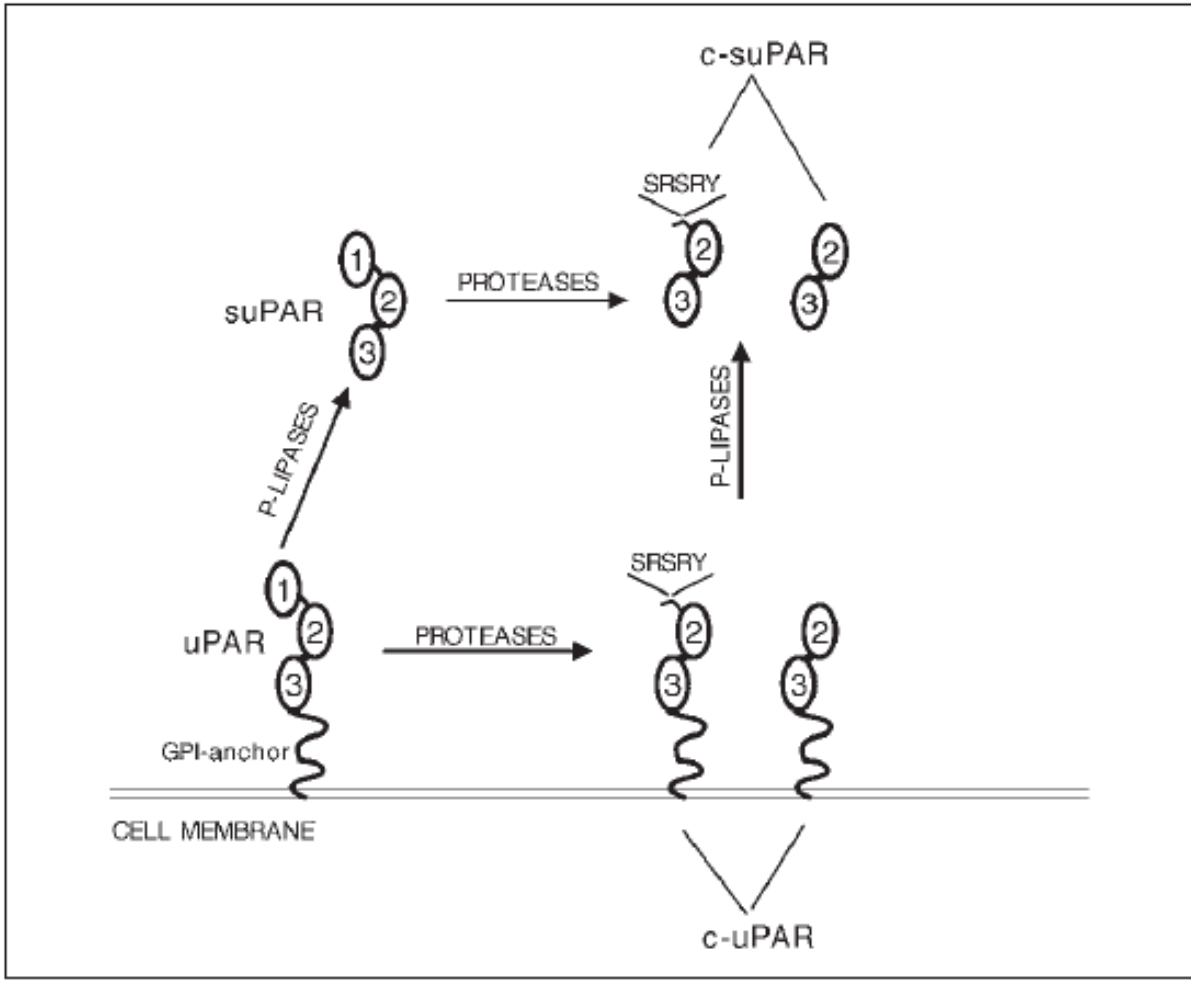


Figure 1: Cell-surface uPAR can be shed by phospho-lipases and/or cleaved by proteases. c-uPAR: cell-anchored cleaved uPAR; suPAR: soluble uPAR; c-suPAR: cleaved soluble uPAR; GPI-anchor: glycosyl-phosphatydil-inositol tail; SRSRY: fMLP-receptor binding site; P-lipases:phospholipases.

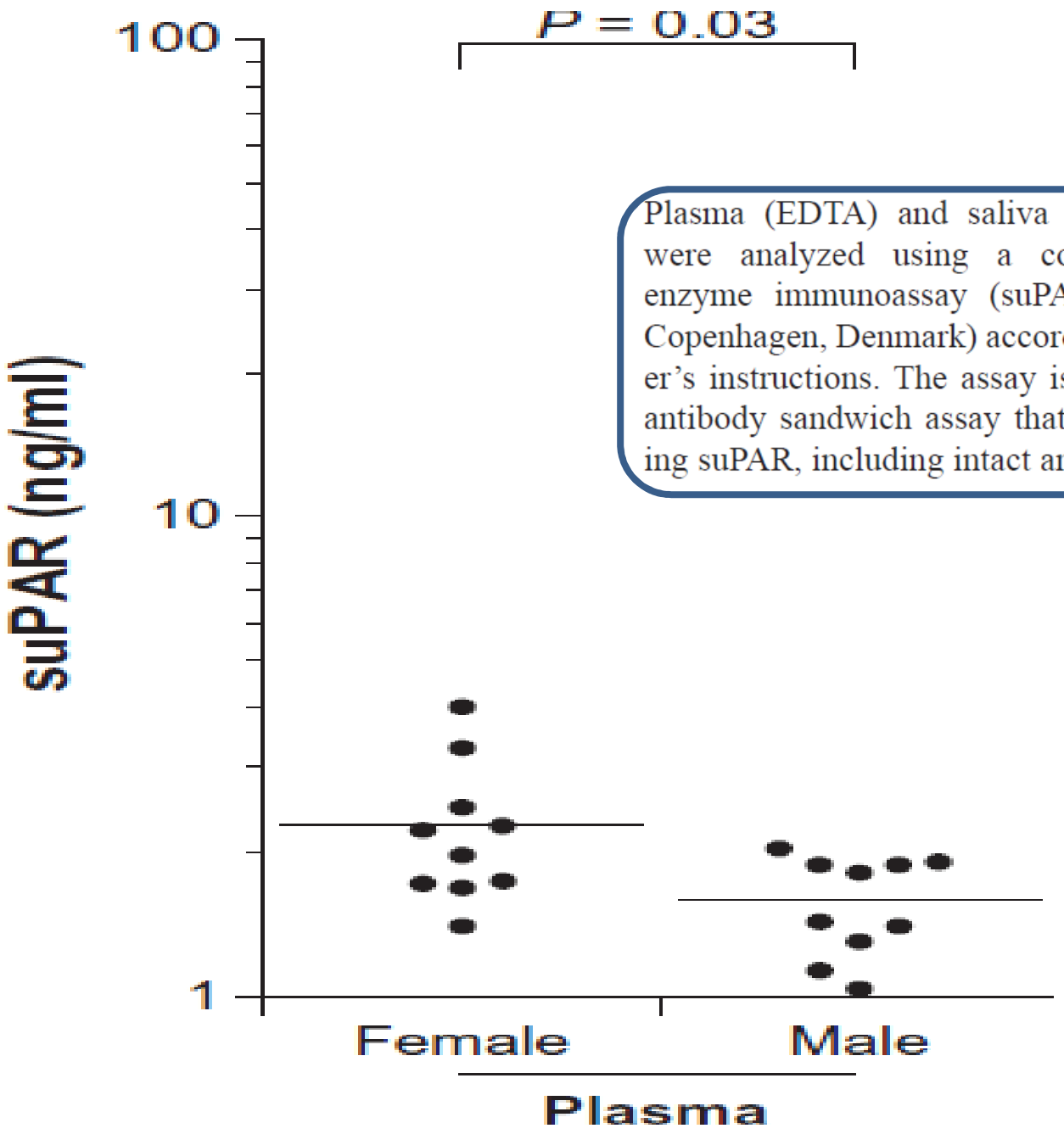
Detection of suPAR in the Saliva of Healthy Young Adults: Comparison with Plasma Levels

Biomarker Insights 2011:6 119–125

Anna Gustafsson, Vjosa Ajeti and Lennart Ljunggren

Table 1. suPAR and CRP in human saliva and blood.

	Male ($n = 10$)			Female ($n = 10$)		
	Range	Median	Mean (±SD)	Range	Median	Mean (±SD)
Age (year)	27–41	35	34 ± 4.8	21–28	25	25 ± 2.8
BMI	25–31	27	28 ± 2.3	18–31	20	21 ± 3.8
Saliva-suPAR (ng/mL)	5.2–68	16	23 ± 19	8.2–43	17	20 ± 12
Plasma-suPAR (ng/mL)	1.0–2.0	1.6	1.6 ± 0.36	1.4–4.0	2.1	2.3 ± 0.81



Plasma (EDTA) and saliva suPAR concentrations were analyzed using a commercially available enzyme immunoassay (suPARnostic™, Virogates, Copenhagen, Denmark) according to the manufacturer's instructions. The assay is a double monoclonal antibody sandwich assay that measures all circulating suPAR, including intact and cleaved forms of the

Wei C et al. Nat Med. 2011

Efekt kliniczny:

- Białkomocz

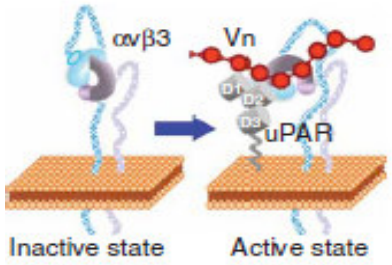
- Zmiany morfologiczne (FSGS)

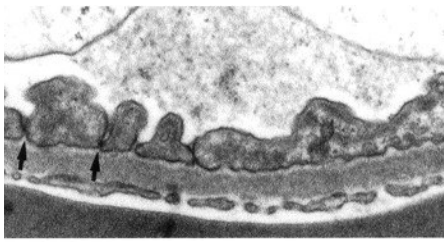
To powoduje uszkodzenie podocyta (stopienie wyrostków)

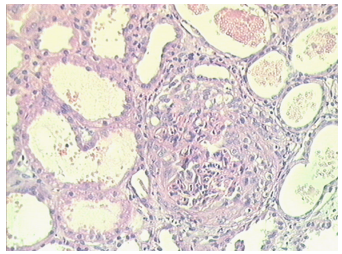
Krążący suPAR

[> 3 ng/ml] nadmiernie

aktywuje integrynę podocyta







Circulating suPAR in two cohorts of primary FSGS.

Wei C, et al. and PodoNet and FSGS CT Study Consortia.

J Am Soc Nephrol. 2012 , 23(12):2051-9

Two cohorts of children and adults with biopsy-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 ($P<0.0001$);

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 ($P=0.04$).

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.

Czy suPAR jest czułym i swoistym wskaźnikiem ?

Activated human neutrophils rapidly release the chemotactically active D2D3 form of the urokinase-type plasminogen activator receptor (uPAR/CD87)

Mol Cell Biochem (2009) 321:111–122

Boris K. Pliyev

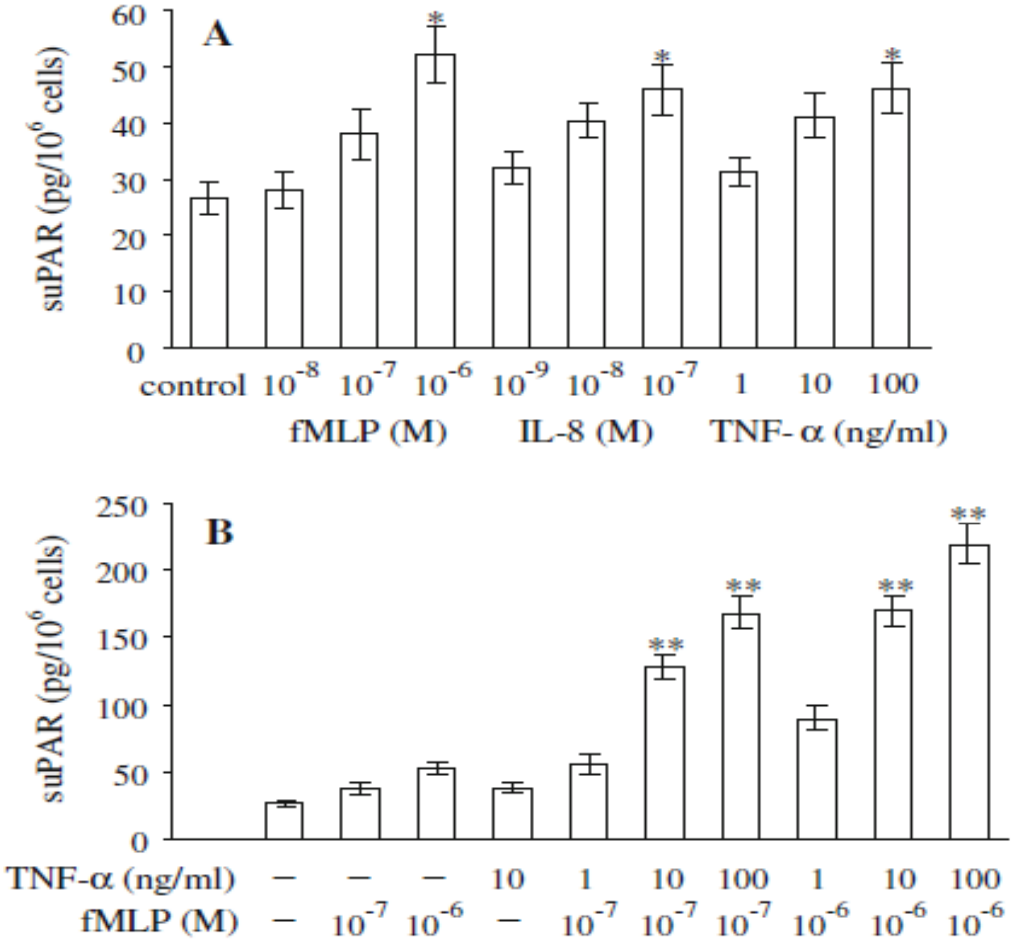
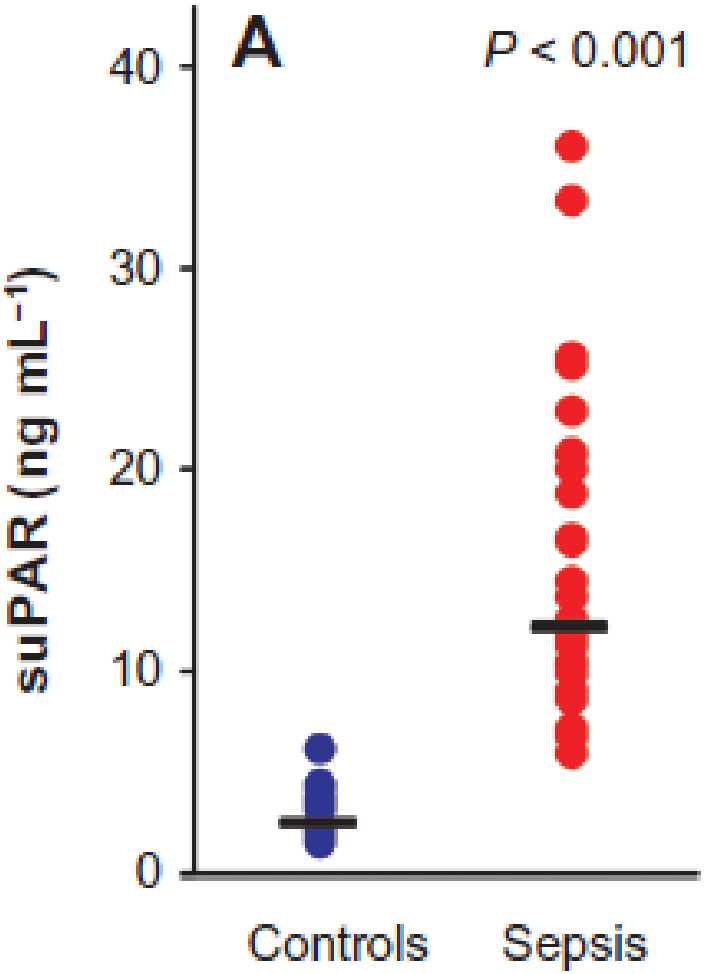


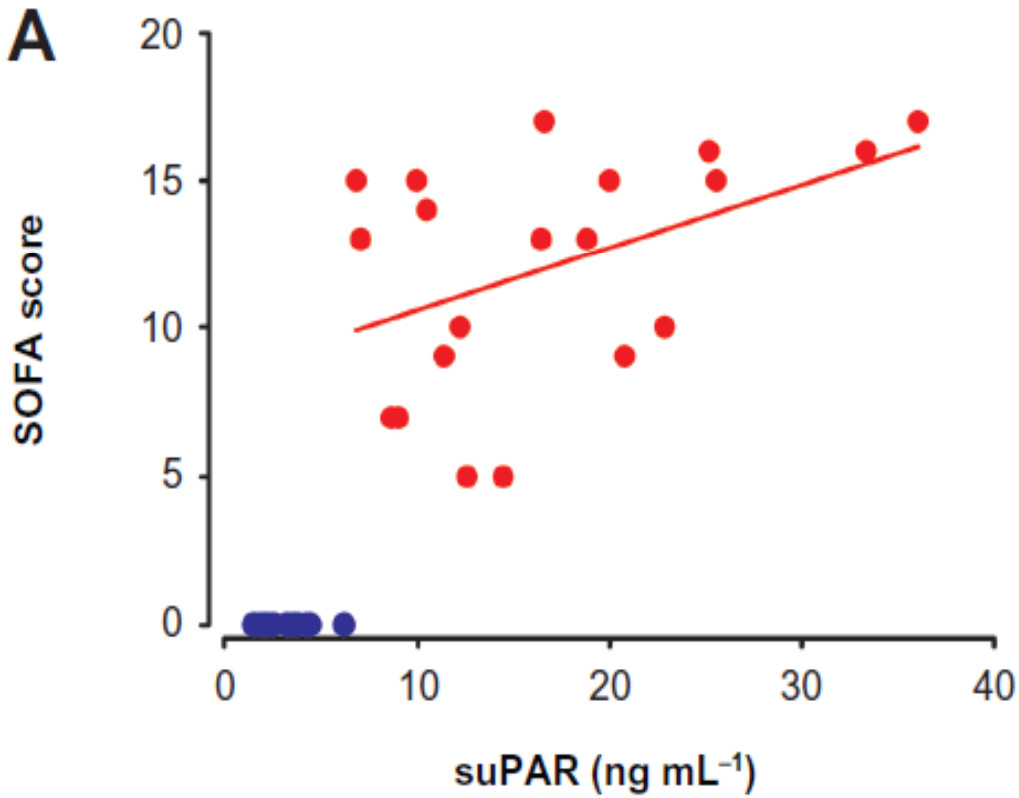
Fig. 2 Inflammatory mediators potentiate suPAR release by human neutrophils. a Effect of fMLP, IL-8 and TNF-α alone on suPAR release by human neutrophils. Cells were unstimulated or incubated for 30 min

The Prognostic Value of suPAR Compared to Other Inflammatory Markers in Patients with Severe Sepsis

Biomarker Insights 2012:7 39–44

Anna Gustafsson[1], Lennart Ljunggren[1], Mikael Bodelsson[2] and Ingrid Berkestedt[2]





Intact and cleaved forms of the urokinase receptor enhance discrimination of cancer from non-malignant conditions in patients presenting with symptoms related to colorectal cancer

AF Lomholt[*,1], G Høyer-Hansen[2], HJ Nielsen[1] and IJ Christensen[2]

British Journal of Cancer (2009) 101, 992–997

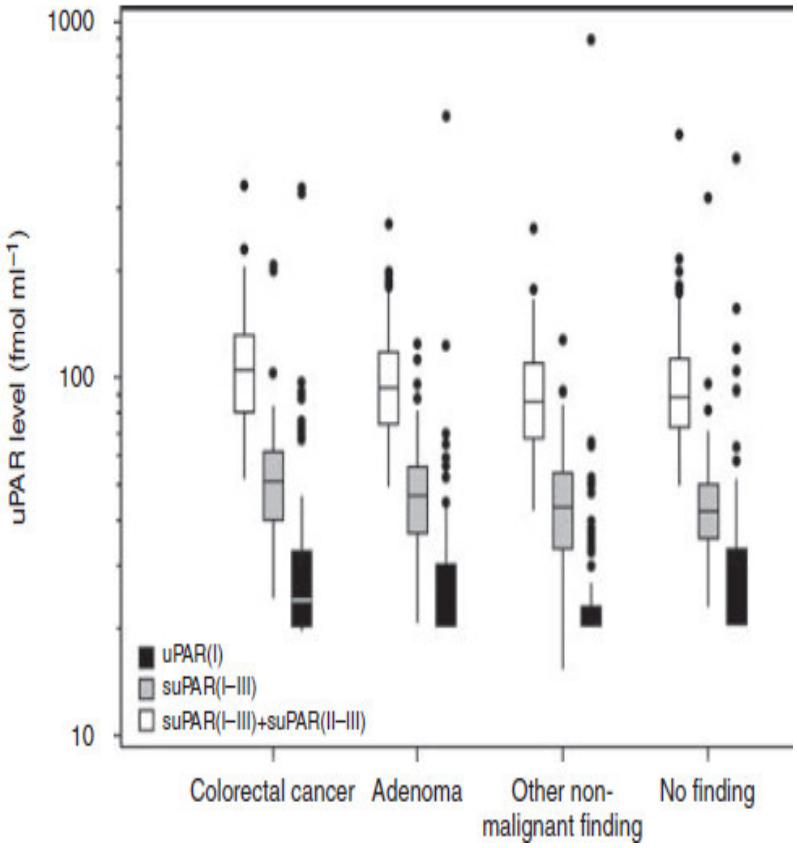


Table 4 Relative mean difference (%) between the diagnostic groups for intact suPAR and intact+cleaved suPAR

Marker	Groups	Relative mean difference and (95% confidence limits in %)	*P*-value
suPAR(I–III)	Non-malignant *vs* No	−3.3 (−13.3–5.8)	0.488
$P=0.002$[a]	Adenoma *vs* no finding	6.4 (−3.4–17.2)	0.208
	Adenoma *vs* ONM finding	9.9 (−0.1–21.0)	0.052
	CRC *vs* adenoma	9.0 (−1.5–18.5)	0.089
	CRC *vs* no finding	17.0 (5.5–29.7)	0.003
	CRC *vs* ONM finding	20.9 (10.2–32.6)	<0.0001
suPAR(I–III)+(II–III)	Non-malignant *vs* No	−6.5 (−17.0–3.1)	0.190
$P=0.004$[a]	Adenoma *vs* no finding	2.3 (−7.2–12.7)	0.653
	Adenoma *vs* ONM finding	8.9 (−0.8–19.5)	0.072
	CRC *vs* adenoma	8.1 (−1.9–17.2)	0.110
	CRC *vs* no finding	11.3 (−0.1–24.0)	0.052
	CRC *vs* ONM finding	18.5 (9.0–28.8)	<0.0001

[a]Results of type III hypothesis tests (ONM = other non-malignant).

A sufficiently powered study including other variables that may influence the uPAR levels (co-morbidity, life style variables) could be conducted measuring uPAR levels in the original study population of more than 5000 individuals. This would allow for an evaluation of the possibility of identifying individuals with a high risk for CRC adjusted for relevant clinical variables and to evaluate uPAR levels in association with other serological biomarkers such as carcinoembryonic antigen and plasma tissue inhibitor of metalloproteinases-1 (Nielsen *et al*, 2007).

Wiarygodna próba:
dopiero > 5000 chorych

Serum Soluble Urokinase-Type Plasminogen Activator Receptor Levels and Idiopathic FSGS in Children: A Single-Center Report.

Bock ME, Price HE, Gallon L, Langman CB.

Clin J Am Soc Nephrol. 2013 Apr 25. [Epub ahead of print]

- 110 samples retrieved from 99 individuals

-20 had primary FSGS, 24 had non-FSGS glomerular disease, 26 had nonglomerular kidney disease, and 29 were healthy controls

-**levels were not significantly different in children with FSGS, non-FSGS glomerular disease, and healthy controls (P>0.05).**

-suPAR levels (median [25%-75%]) were higher in children with nonglomerular kidney disease (3385 pg/ml [2695-4392]) versus FSGS (2487 pg/ml [2191-3351]; P<0.05).

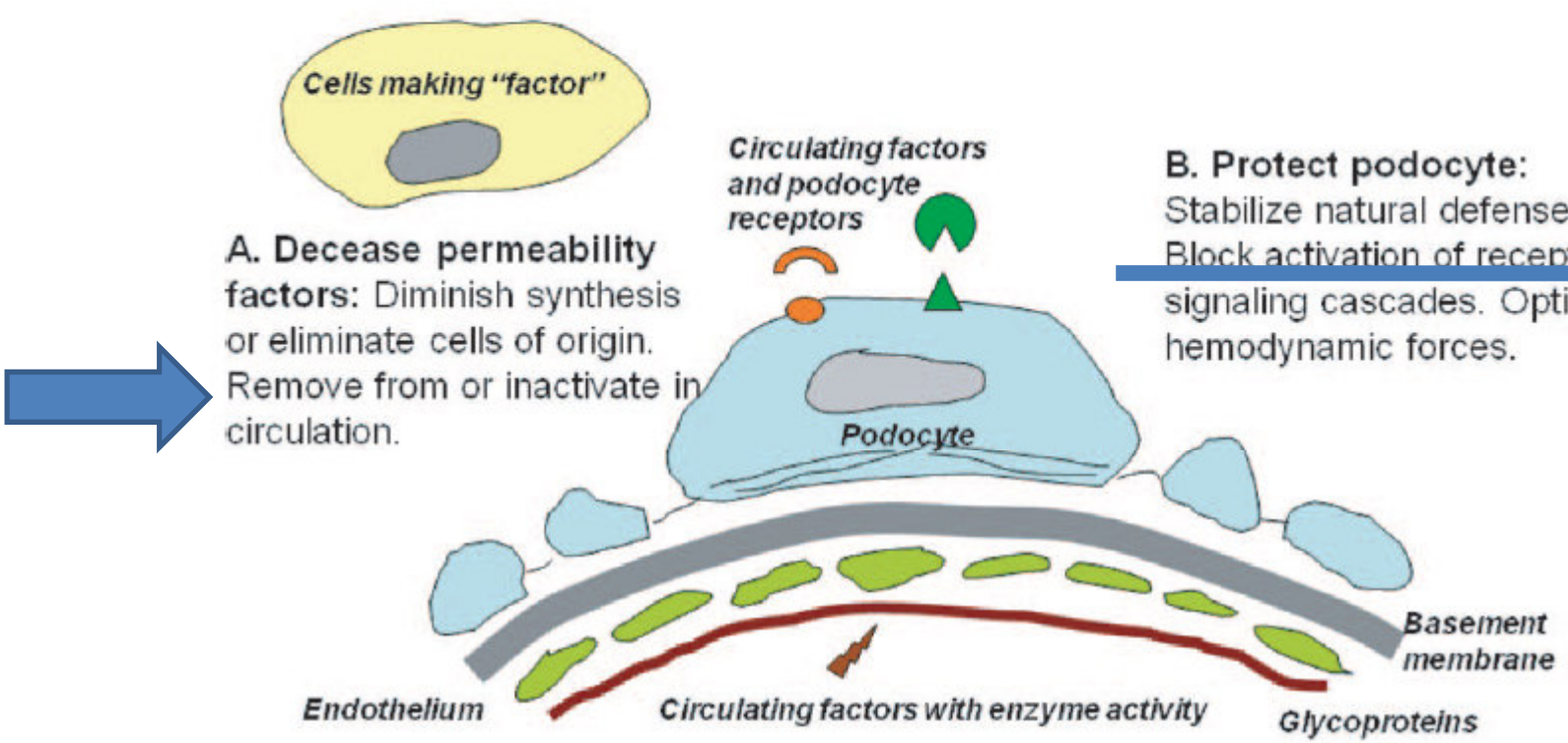
-suPAR levels in all female participants were lower than in male participants (P=0.03).

CONCLUSIONS:

On the basis of these results, circulating suPAR is unlikely the leading cause for childhood idiopathic FSGS

Co wynika ze znajomości suPAR dla leczenia chorych z FSGS ?

Strategies for therapy in nephrotic syndrome



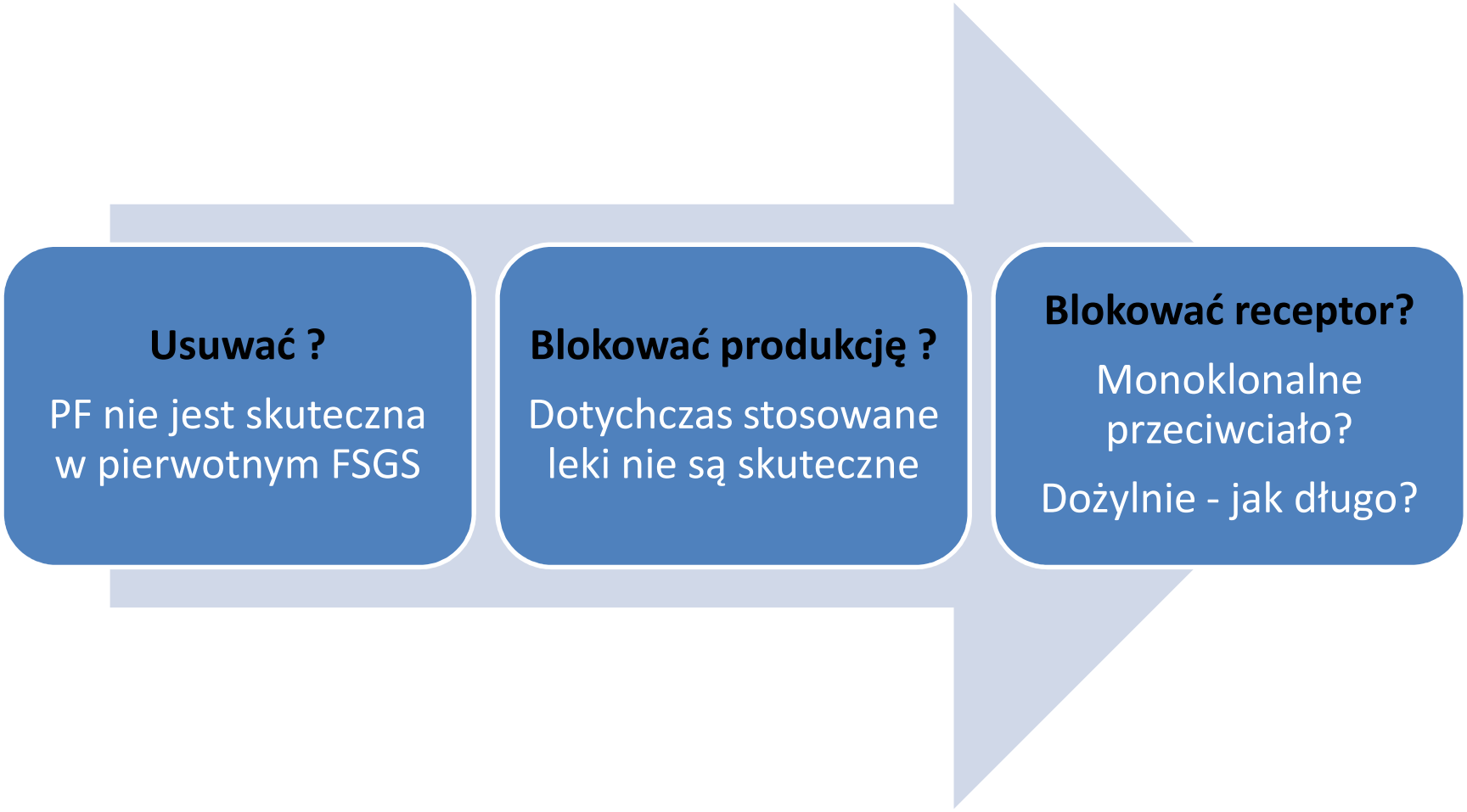
A. Decease permeability factors: Diminish synthesis or eliminate cells of origin. Remove from or inactivate in circulation.

B. Protect podocyte: Stabilize natural defenses. Block activation of receptors, signaling cascades. Optimize hemodynamic forces.

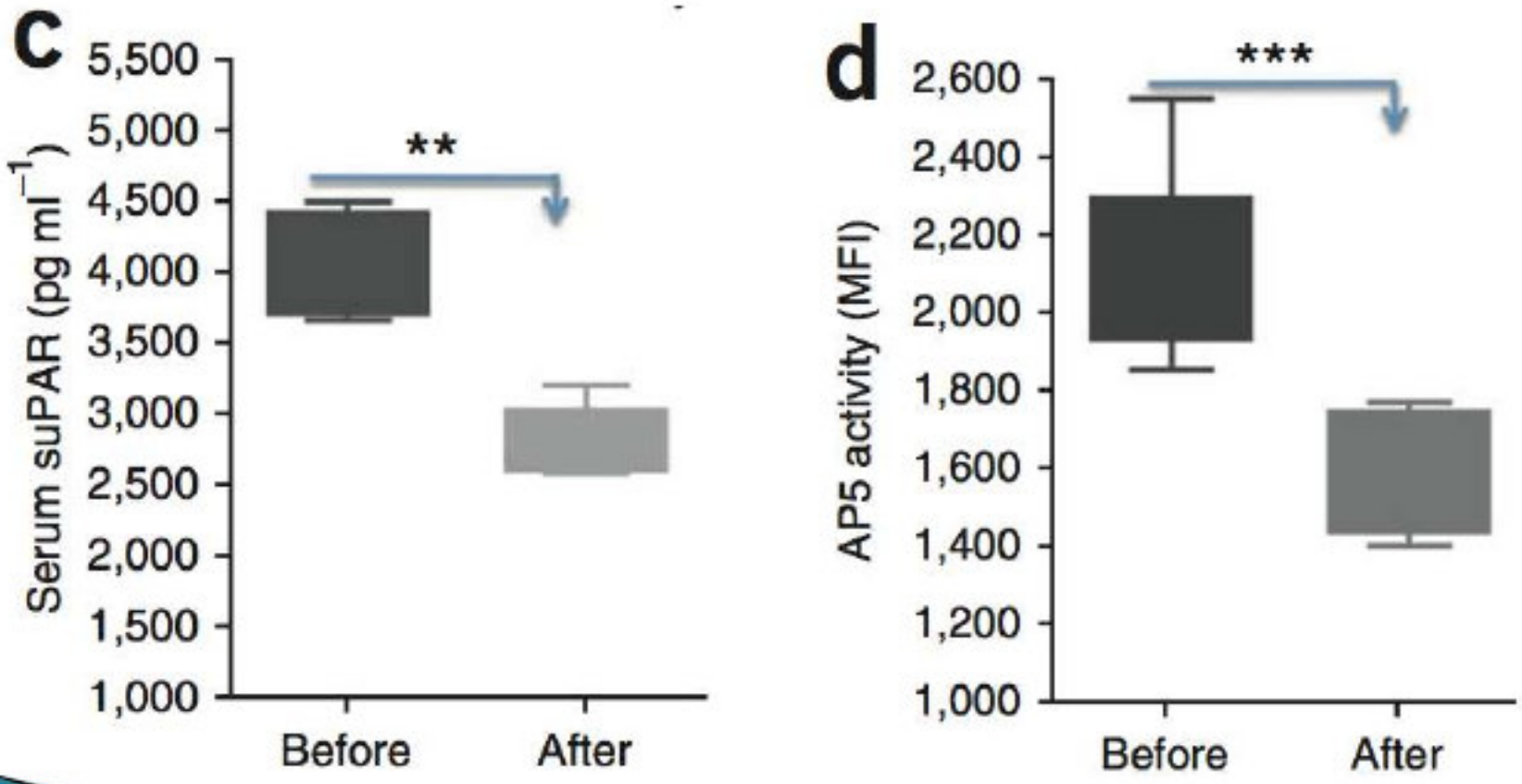
C. Protect endothelium: Block glycoprotein digestion. Optimize VEGF and antioxidants.

D. Protect kidney: Use anti-inflammatory and antifibrotic strategies. Control lipids.

Jak walczyć z suPAR ?



suPAR concentration and podocyte $ß_3$ integrin activity decrease with Plasmapharesis in recurrent FSGS

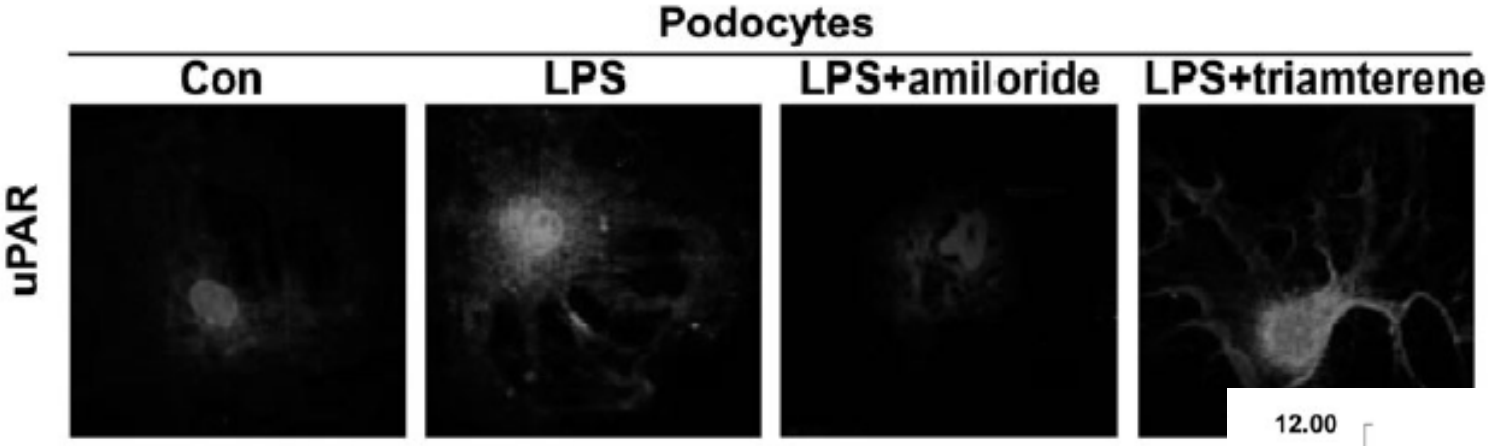


Amiloride off-target effect inhibits podocyte urokinase receptor expression and reduces proteinuria

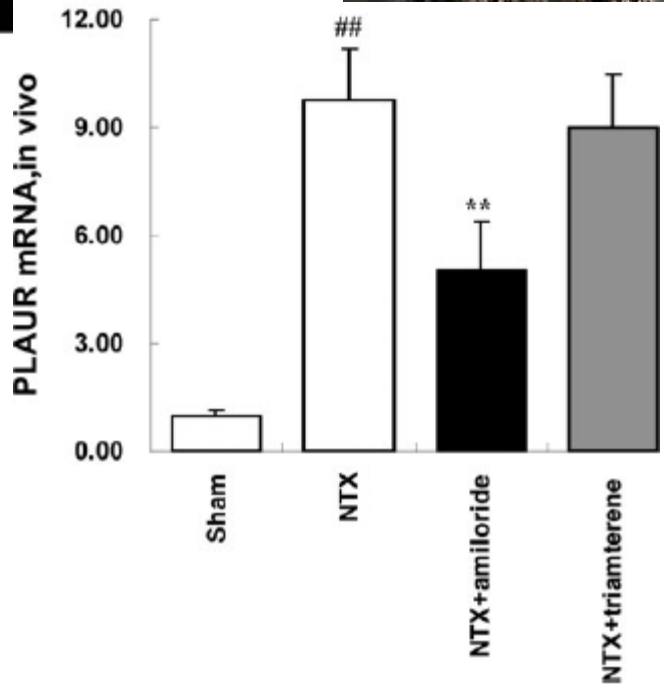
Nephrol Dial Transplant (2012) 27: 1746–1755

Bin Zhang[1,2,*], Shaoting Xie[1,2,*], Wei Shi[1] and Yun Yang[1]

Our patient

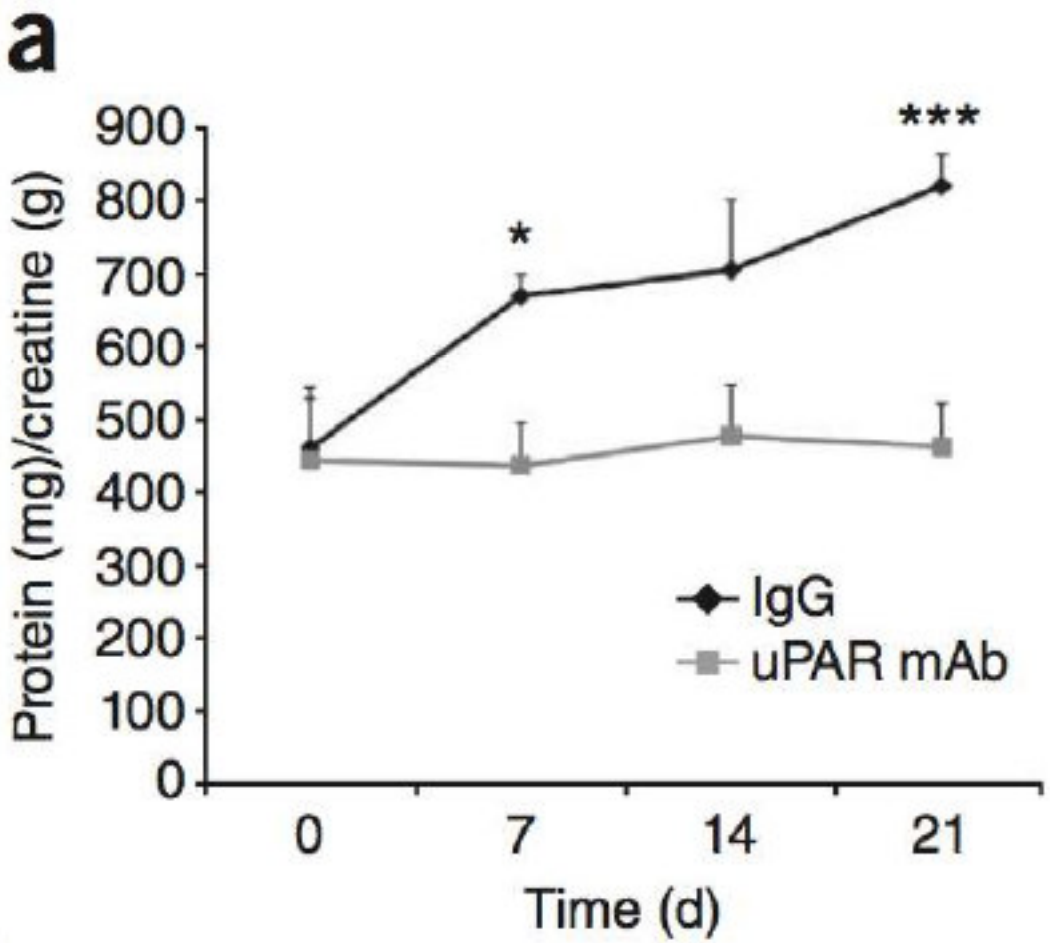


Amiloride treatment inhibits uPAR induction in podocytes *in vivo*.



In conclusion, we provide here the experimental basis for a therapeutic benefit of amiloride in podocyte dysfunction or proteinuria that can readily be used in the clinics as adjunct therapy with other anti-proteinuric modalities.

uPAR mAb blocks suPAR binding to $ß_3$ integrin and reduces proteinuria



Podsumowanie I

- Wykrycie obecności w podocycie receptora urokinazowego aktywatora plazminogenu (uPAR) oraz jego rozpuszczalnej krążącej postaci (suPAR) jest ważnym krokiem w badaniach podstawowych, o potencjalnych implikacjach klinicznych
- Nie jest to „święty Graal”, bowiem ok. 1/3 chorych z FSGS ma prawidłowe stężenie suPAR, a oprócz niego w krążeniu identyfikuje się inne liczne substancje biologiczne, które mają znaczenie dla powstawania i przebiegu klinicznego FSGS
- Wiarygodność predykcyjna oraz rozkład prawidłowego stężenia suPAR wymaga oznaczenia tego parametru u kilku tysięcy (a nie kilku setek) osób.
- Na razie nie wiadomo, jakie dokładnie działanie terapeutyczne powinno być ukierunkowane na obniżenie stężenia suPAR , jak długo będzie działać i co z tego wyniknie w praktyce
- Im więcej publikacji o suPAR u dzieci z FSGS, tym więcej wątpliwości

Niemniej –nefrologia jest SUPAR !