FSGS

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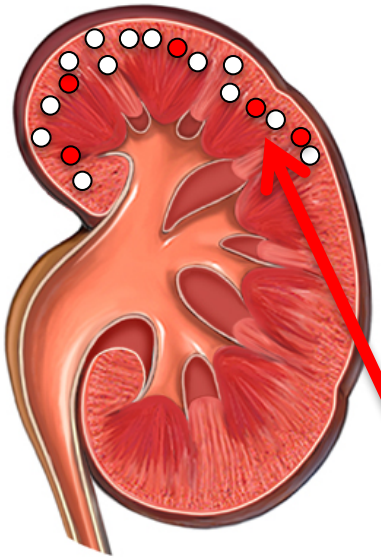
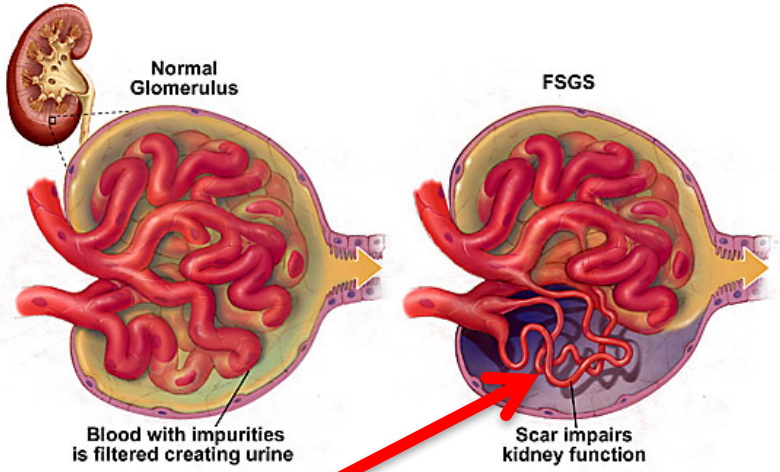
„FSGS is a lesion, not a disease“

Nachman PH and Glassock RJ, in: NephSAP Vol 11, No 3, 2012





Focal Segmental Glomerulosclerosis

Σκληρός = hard

Causes of FSGS

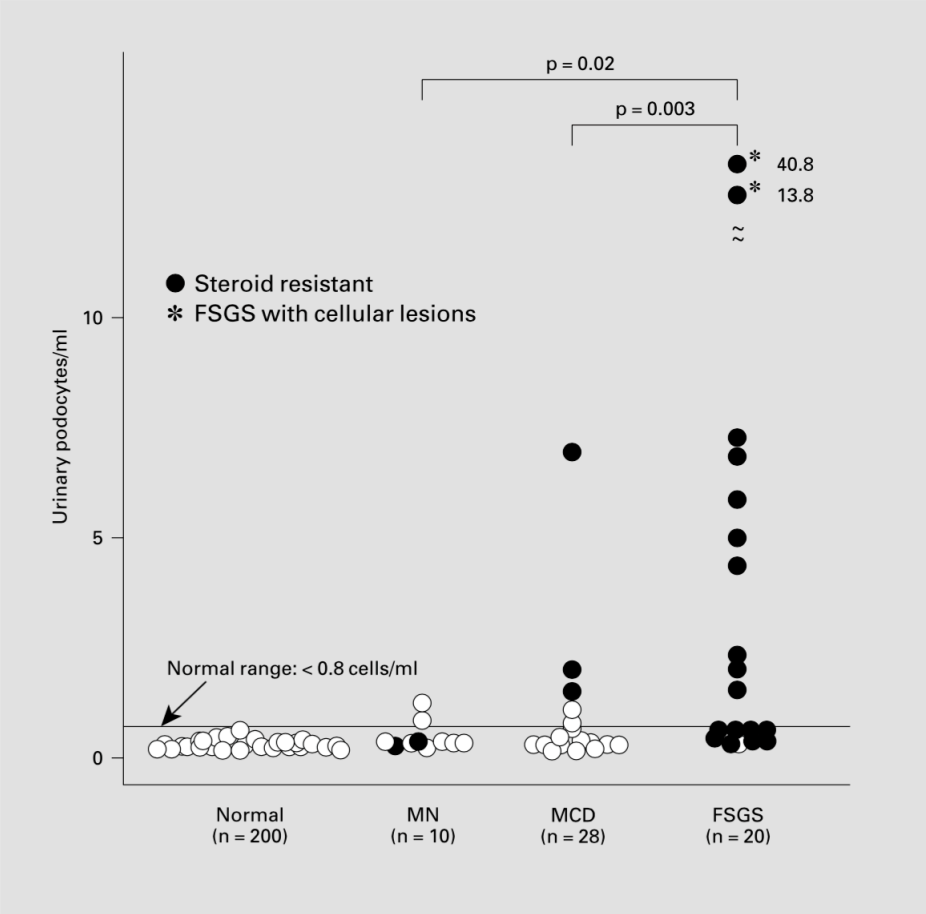
Table 1. Causes of Focal Segmental Glomerulosclerosis.

Type of Disease	Cause
Primary (idiopathic) form	Specific cause unknown; mediated by circulating permeability factors
Secondary forms	
Familial or genetic	Mutations in specific podocyte genes*
Virus-associated	Human immunodeficiency virus type 1, parvovirus B19, simian virus 40, cytomegalovirus, Epstein–Barr virus
Drug-induced	Heroin; interferons alfa, beta, and gamma; lithium; pamidronate; sirolimus; calcineurin-inhibitor nephrotoxicity; anabolic steroids
Adaptive†	Conditions with reduced renal mass: oligomeganephronia, very low birth weight, unilateral renal agenesis, renal dysplasia, reflux nephropathy, sequela to cortical necrosis, surgical renal ablation, renal allograft, aging kidney, any advanced renal disease with reduced functioning nephrons Conditions with initially normal renal mass: systemic hypertension, acute or chronic vaso-occlusive processes (atheroembolization, thrombotic microangiopathy, renal-artery stenosis), elevated body-mass index (obesity, increased lean body mass [e.g., bodybuilding]), cyanotic congenital heart disease, sickle cell anemia

D'Agati VD et al. NEJM 2011;365:2398

+ secondary focal and segmental glomerulosclerotic lesions in most kinds of kidney diseases!

Pathogenesis of FSGS: the podocyte depletion hypothesis



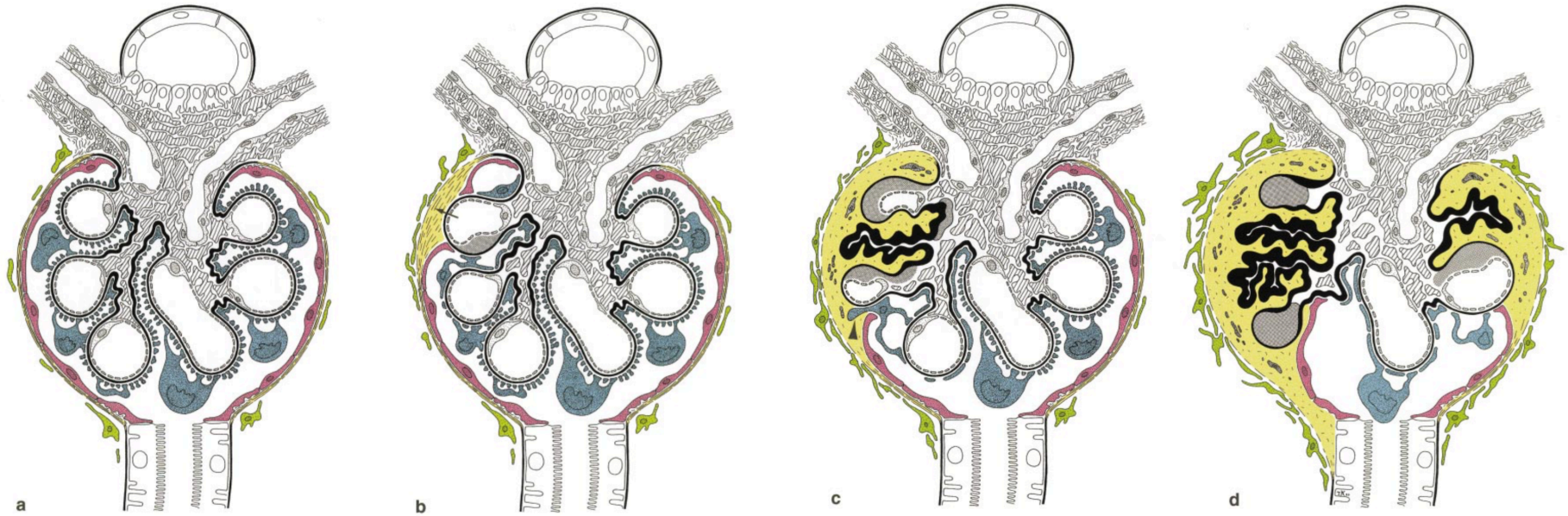
Hara et al., Nephron 2001;89:342

Kidney International, Vol. 54 (1998), pp. 687–697

PERSPECTIVES IN BASIC SCIENCE

Progression of glomerular diseases: Is the podocyte the culprit?

WILHELM KRIZ, NORBERT GRETZ, and KEVIN V. LEMLEY

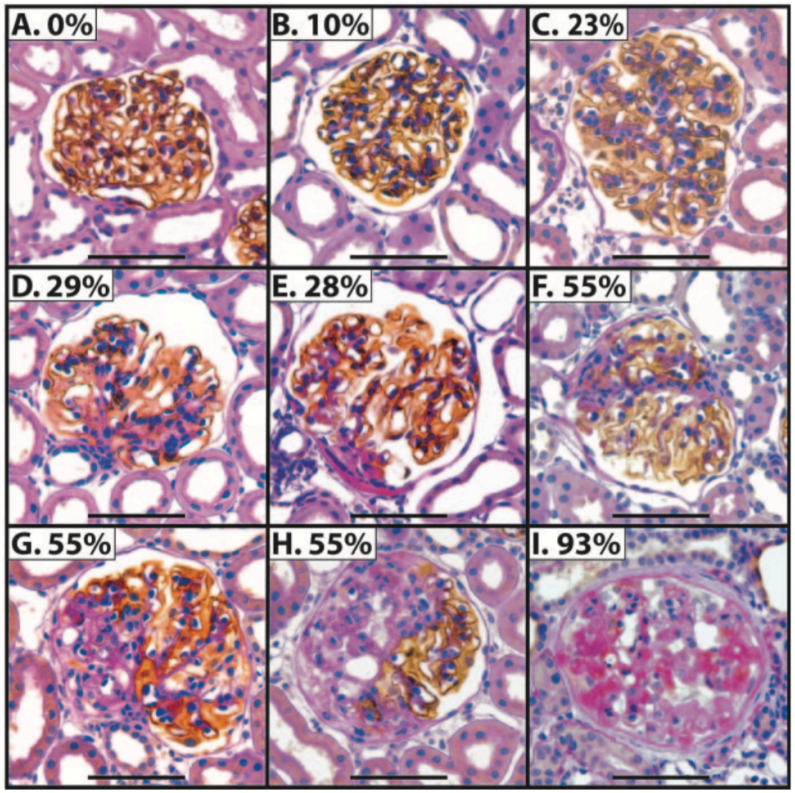


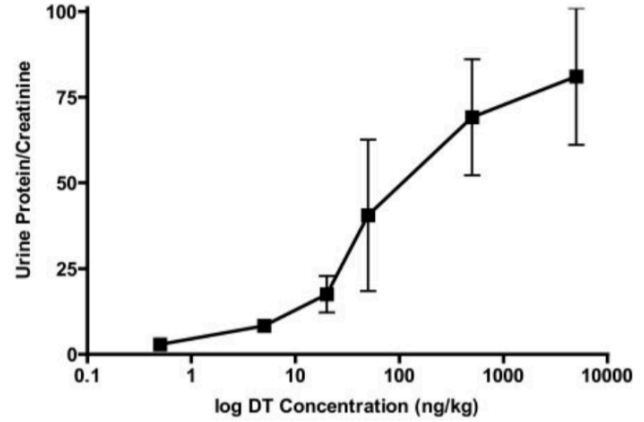
„adhesion“

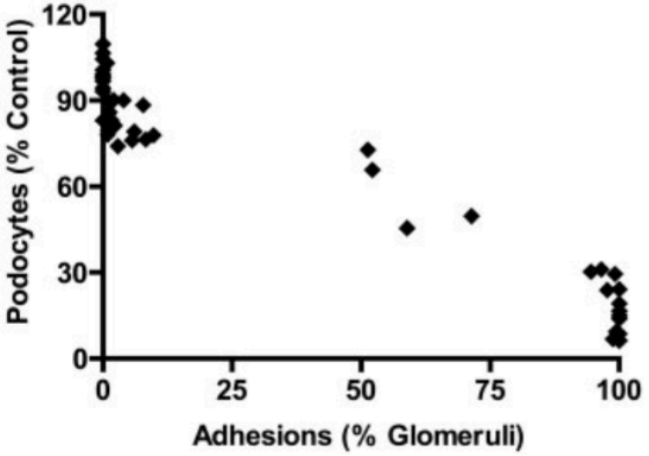
sclerosis

progression of the lesion

Podocyte depletion hypothesis:
loss of >20% of podocytes leads to FSGS

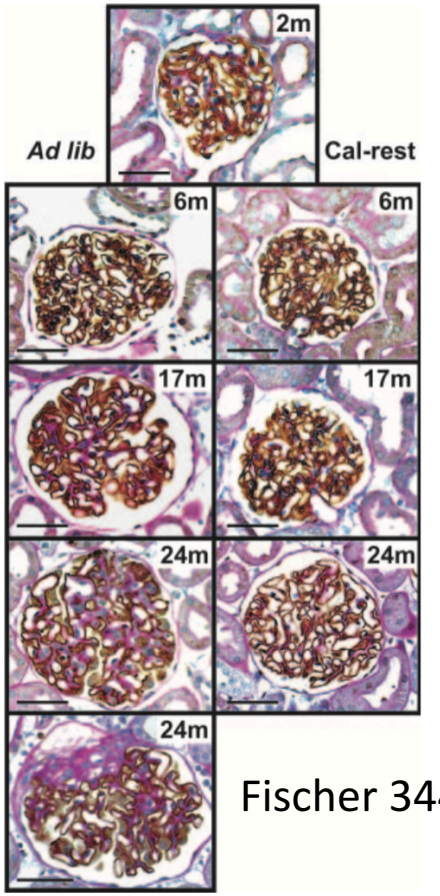






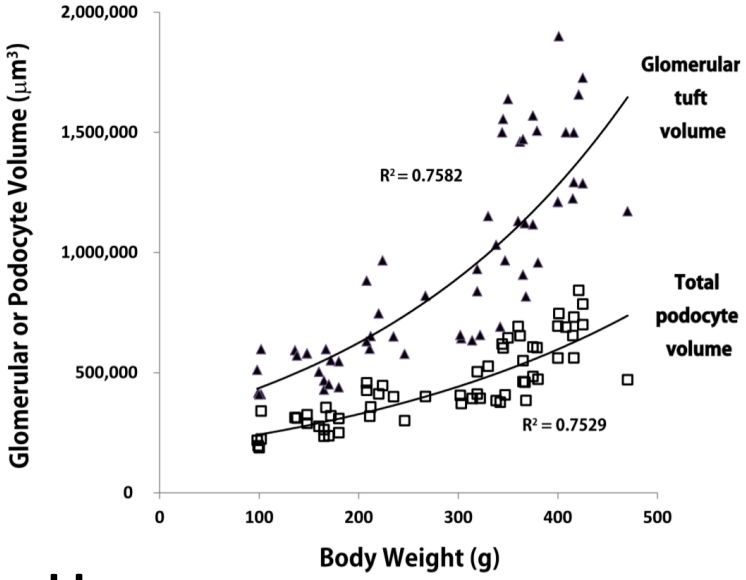
Wharram et al., JASN 2005;16:2941

Mismatch between podocyte number and glomerular tuft volume leads to FSGS



Fischer 344 rats

Wiggins, JASN 2005;16:2953



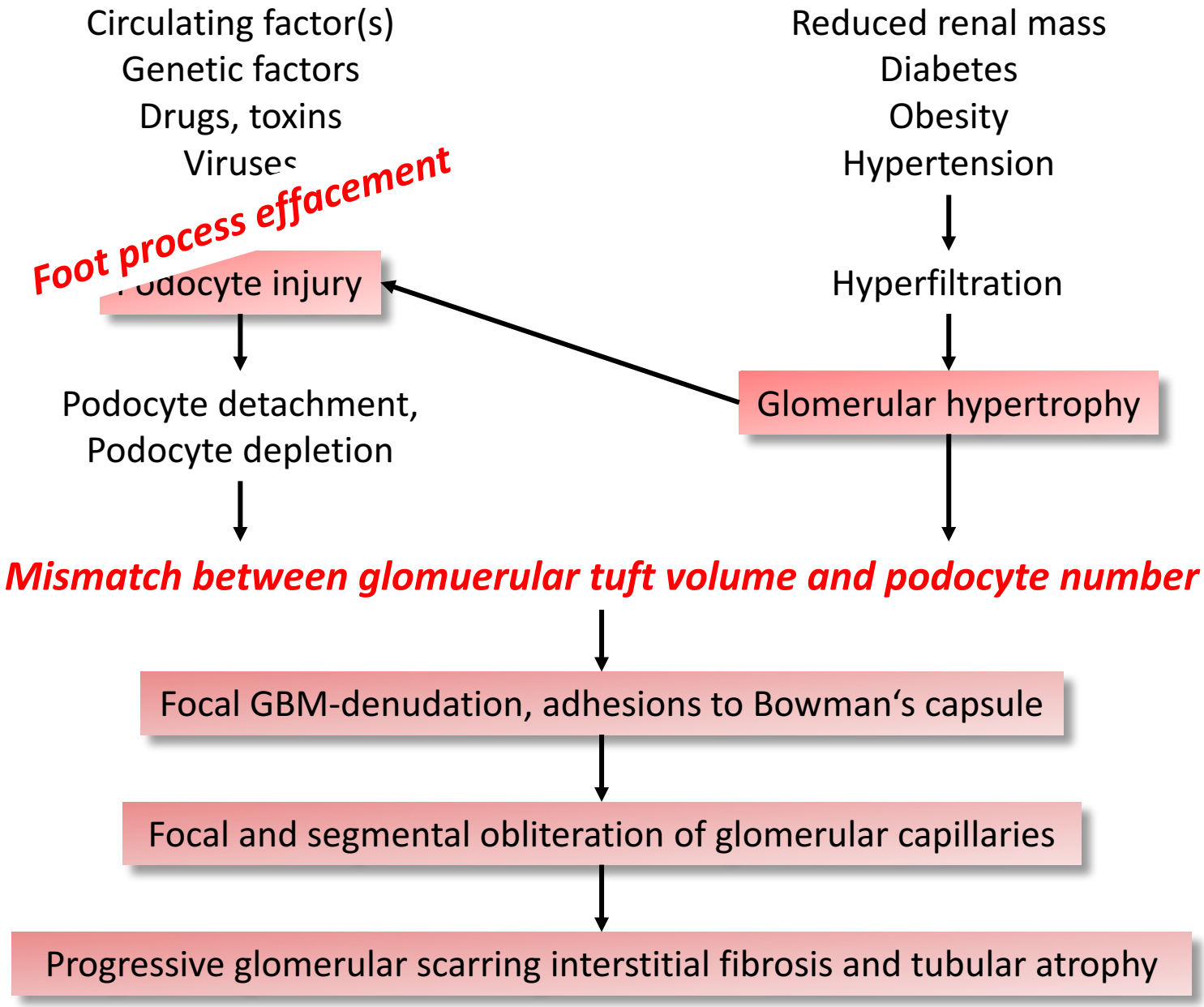
FSGS induced by:

- *Spontaneous glomerulomegaly (aging)*
- *Uninephrectomy*
- *Genetic mTOR inhibition*

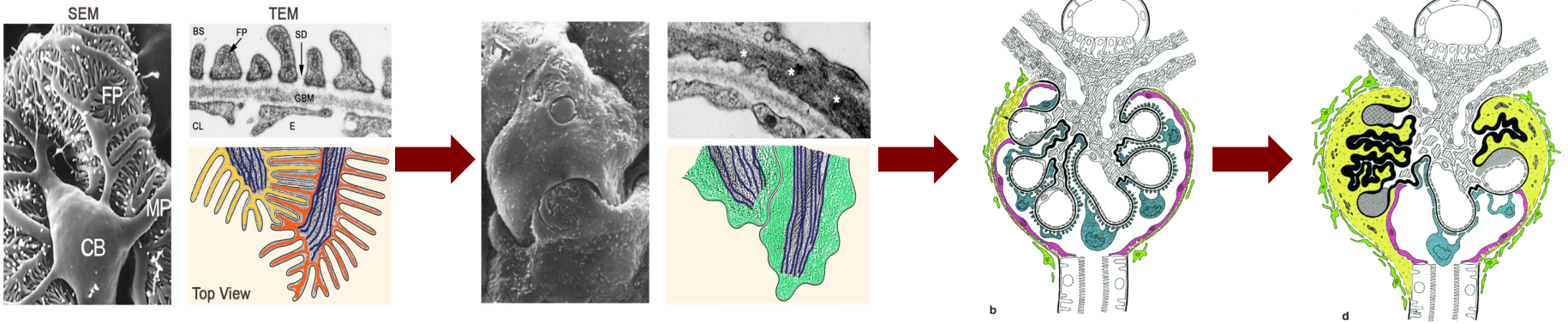
Calorie restriction prevented:

- *Glomerular enlargement*
- *Sclerotic lesions*
- *Proteinuria*
- *Renal failure*

Fukuda, JASN 2012;23:1351


Circulating factor(s)
Genetic factors
Drugs, toxins
Viruses
Reduced renal mass
Diabetes
Obesity
Hypertension
Foot process effacement
Podocyte injury
Hyperfiltration
Podocyte detachment,
Podocyte depletion
Glomerular hypertrophy
Mismatch between glomuerular tuft volume and podocyte number
Focal GBM-denudation, adhesions to Bowman's capsule
Focal and segmental obliteration of glomerular capillaries
Progressive glomerular scarring interstitial fibrosis and tubular atrophy

Foot process effacement



healthy podocytes

Foot process effacement

Podocyte detachment
Podocyte depletion
GBM denudation
Adhesions

Glomerulosclerosis

reversible

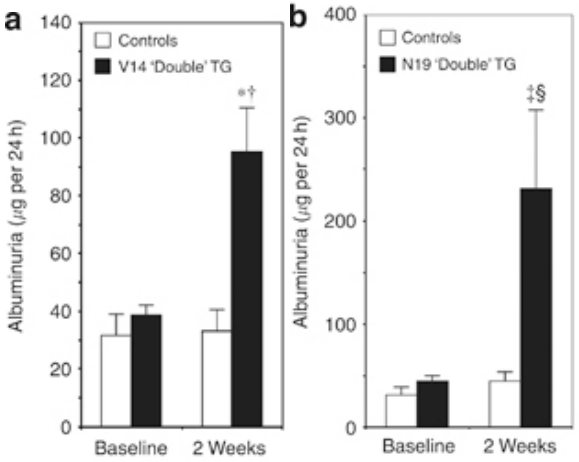
Irreversible

Is foot process effacement...

... an unspecific sign of podocyte damage / stress?

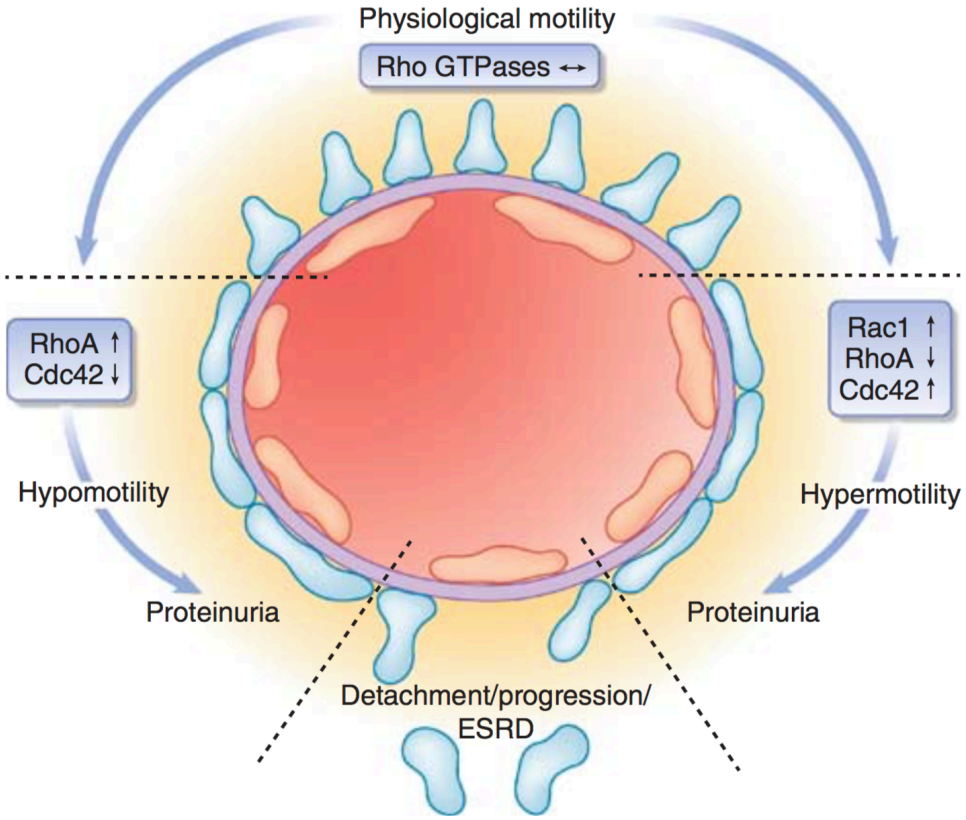
... or a specific reaction of podocytes to prevent detachment?

Podocyte motility and FP effacement



overactive RhoA

inactive RhoA

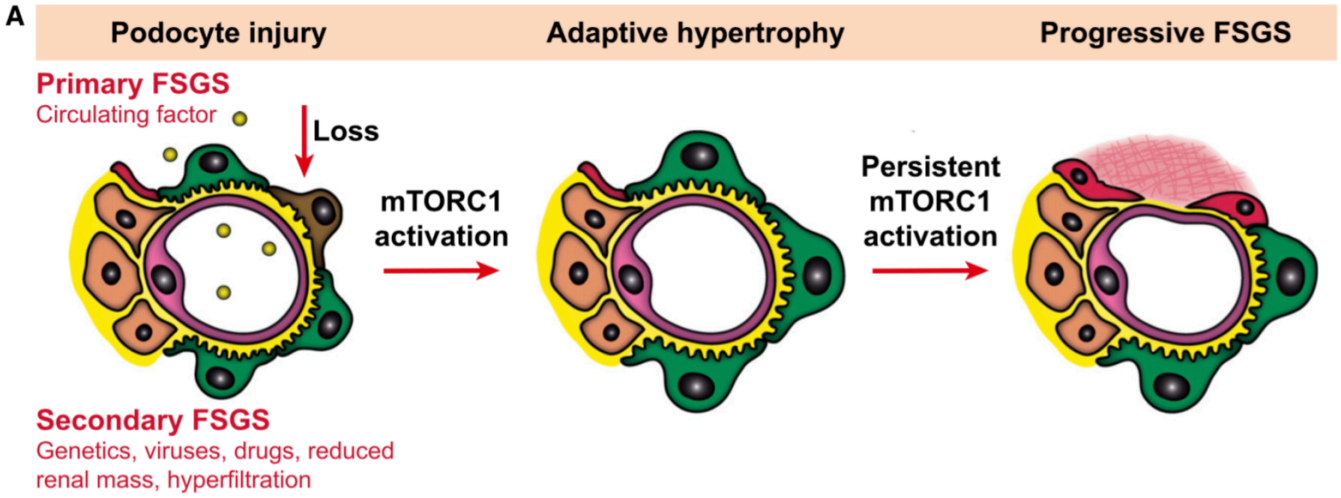


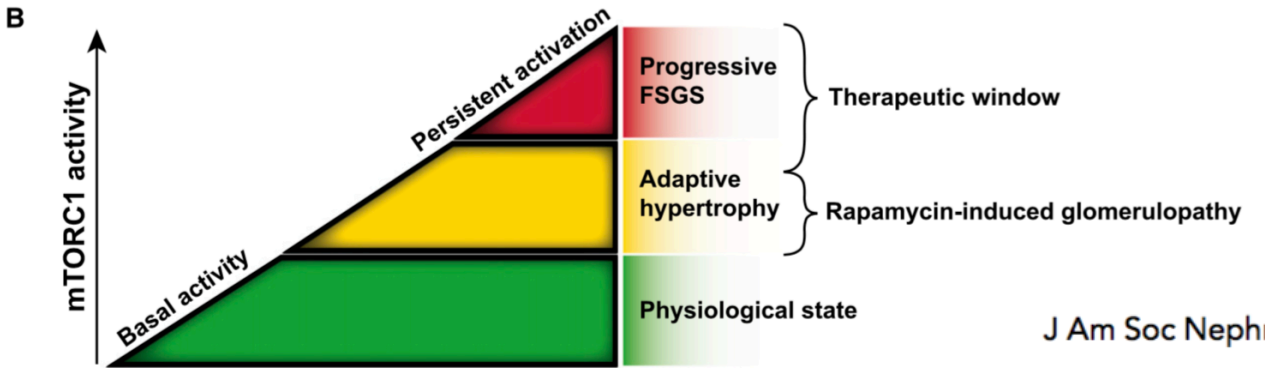
Wang, Kidney Int 2012;81:1075

Kistler, Kidney Int. 2012;81:1053

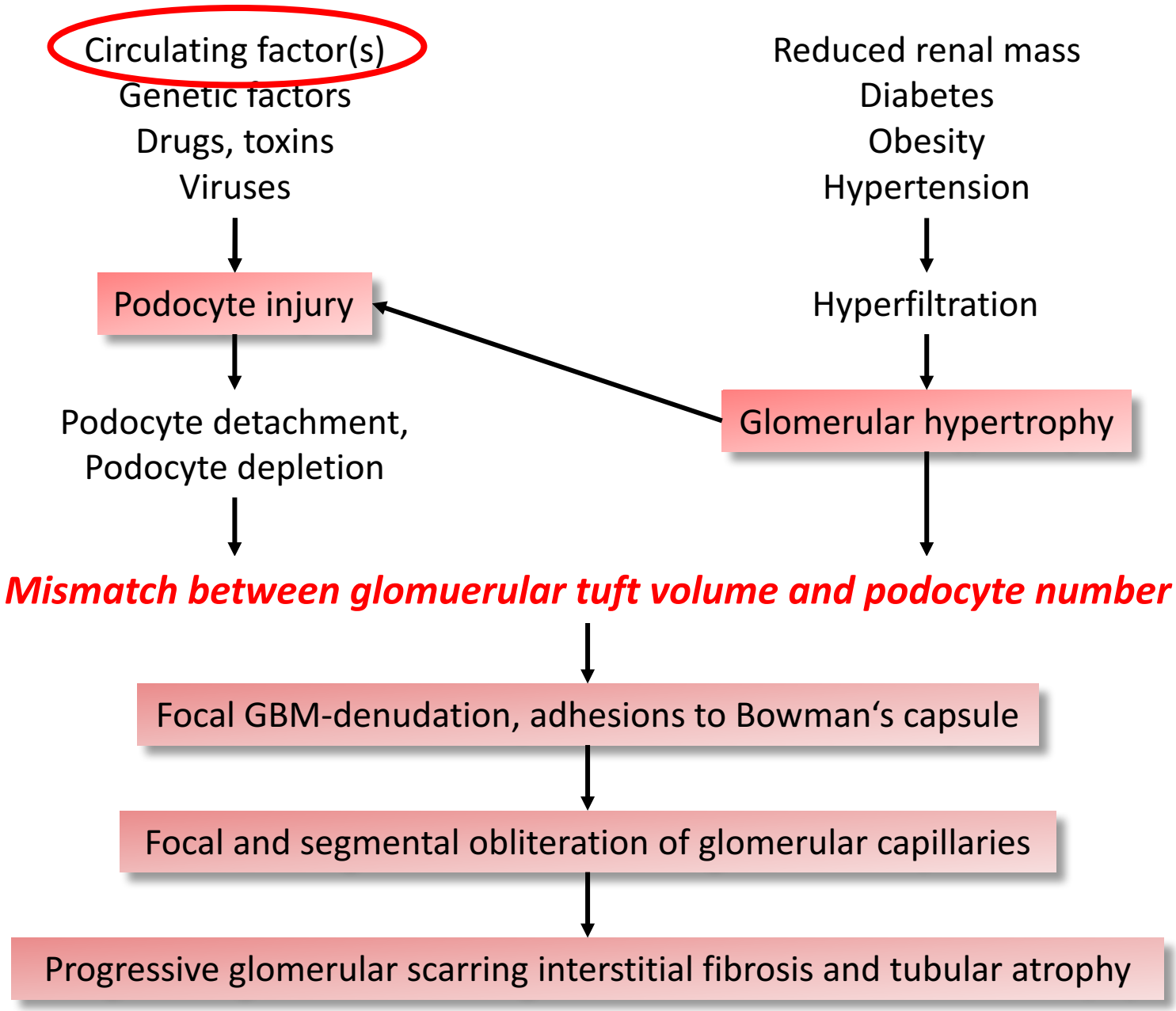
Targeting mTOR Signaling Can Prevent the Progression of FSGS

Stefan Zschiedrich,* Tillmann Bork,* Wei Liang,*† Nicola Wanner,* Kristina Eulenbruch,* Stefan Munder,* Björn Hartleben,* Oliver Kretz,*‡ Simon Gerber,§ Matias Simons,§ Amandine Viau,* Martine Burtin,‖ Changli Wei,¶ Jochen Reiser,¶ Nadja Herbach,** Maria-Pia Rastaldi,†† Clemens D Cohen,‡‡ Pierre-Louis Tharaux,§§ Fabiola Terzi,‖ Gerd Walz,* Markus Gödel,* and Tobias B Huber*‡‖‖¶¶





J Am Soc Nephrol **28:** ●●●–●●●, 2017


Circulating factor(s)
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Focal GBM-denudation, adhesions to Bowman‘s capsule
Focal and segmental obliteration of glomerular capillaries
Progressive glomerular scarring interstitial fibrosis and tubular atrophy

Circulating permeability factor hypothesis

- FSGS-recurrence post-transplant within hours
  Hoyer, Lancet 1972;2:343
- FSGS-recurrence responds to PEX
  Artero, AJKD 1994,23:574
- FSGS patient serum causes proteinuria in rats
  Zimmerman, Clin Nephrol 1984;22:32
- FSGS patient serum increases albumin permeability of isolated glomeruli in vitro
  Savin, NEJM 1996;334:878
- Successful retransplantation of a kidney after post-transplant FSGS recurrence
  Gallon, NEJM 2012;366:1648

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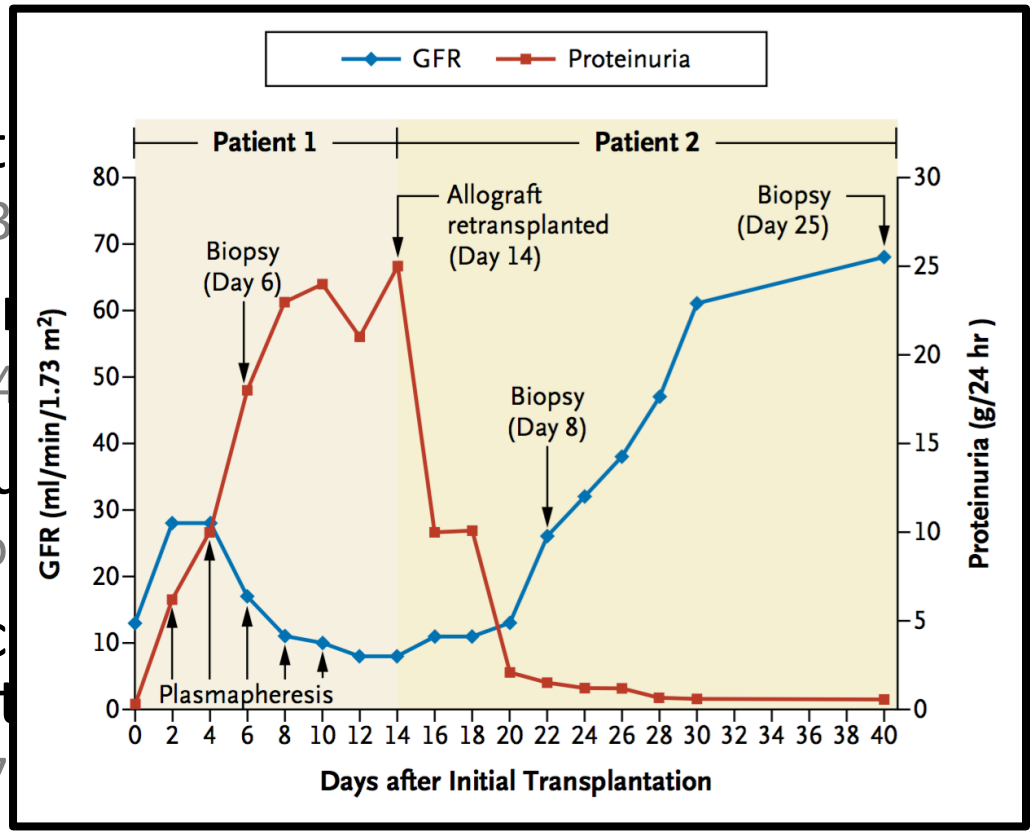


Cardiotrophin-like cytokine-1 (CLC-1)

- Identified by chromatography of plasma from a patient with recurrent FSGS
- Increases albumin permeability of isolated glomeruli in vitro
- Induces proteinuria when injected into rats
- Binds to galactose: novel treatment for FSGS?

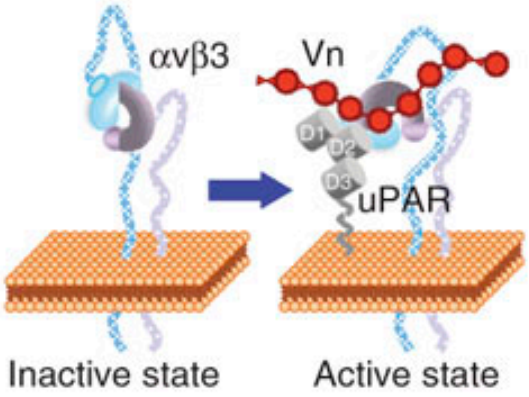
But: 2 small studies both negative (or inconclusive)
RCT in adults with FSGS (7 control / 7 galactose / 7 adalimumab)
case series (7 children with SRNS)

Savin VJ et al. ASN 2008 (abstract)

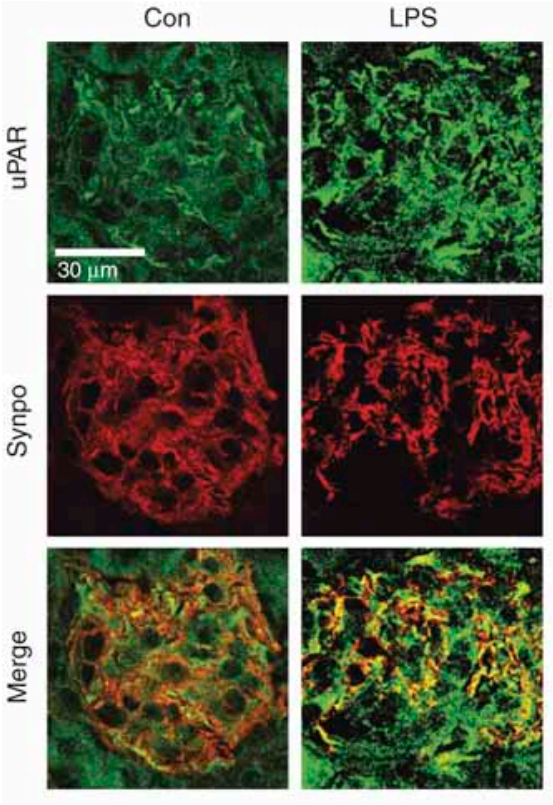
Trachtman, BMC Nephrol 2015;16:111 and Sgambat Pediatr Nephrol 2013;28:2131

suPAR
soluble urokinase-type plasminogen activator receptor

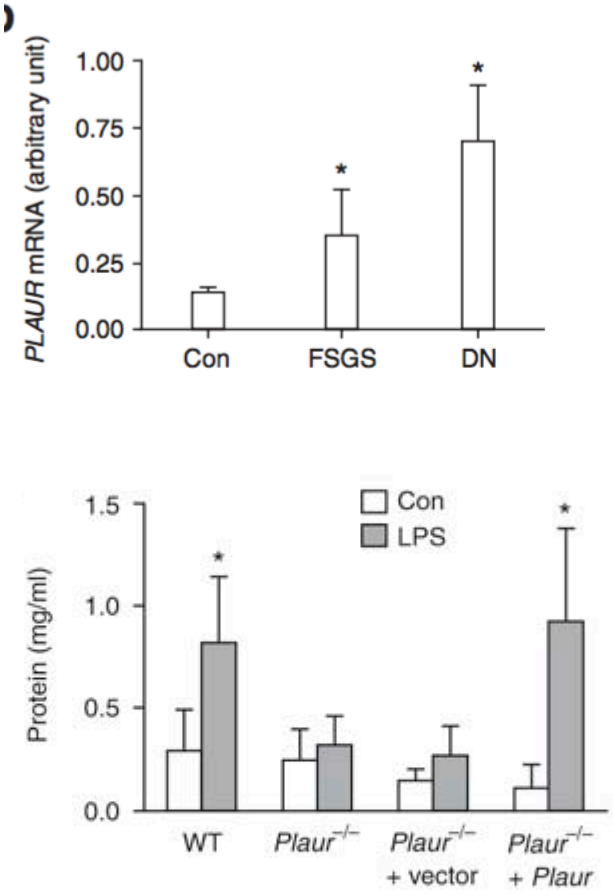
uPAR



uPAR activates β3-integrin



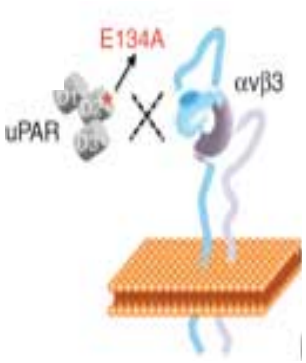
Podocyte uPAR expression upregulated in a mouse model of proteinuria and in human FSGS and DN

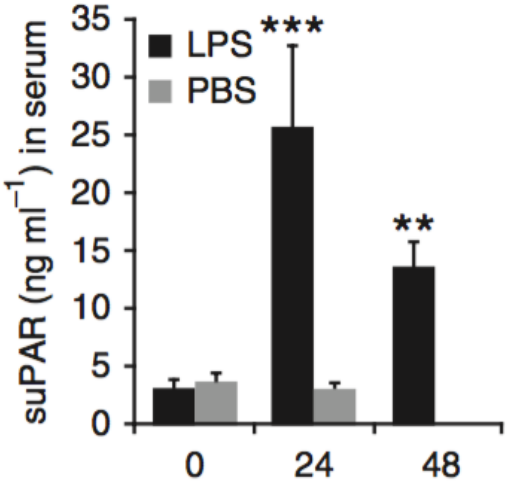


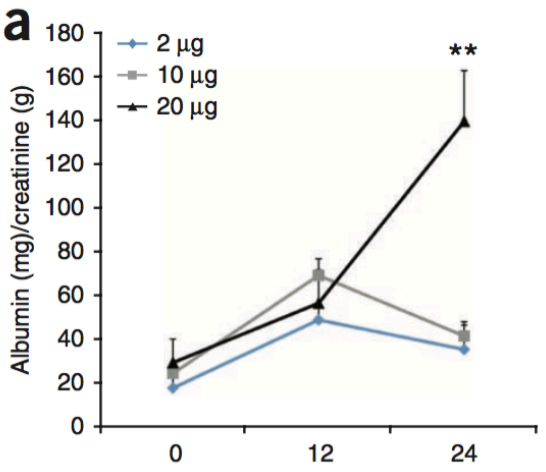
uPAR $^{-/-}$ mice are protected from proteinuria

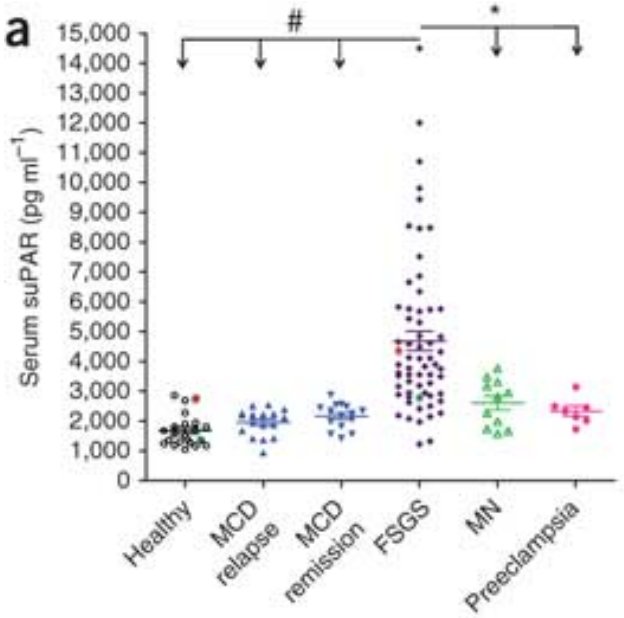
Wei, Nat Med. 2008;14:55

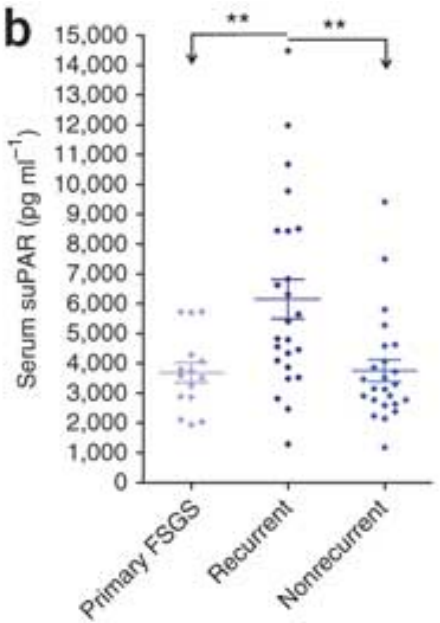
suPAR











Wei, Nat Med 2011;17:952

Is suPAR the FSGS-permeability factor?

- Large overlap of suPAR levels between FSGS and healthy controls
- Pretransplant suPAR levels do not clearly predict relapse of FSGS
- Elevated suPAR is not specific for primary FSGS
  - suPAR elevated in genetic FSGS
  - suPAR elevated in diabetic kidney disease and other CKD
  - suPAR elevated in cancers (without proteinuria)
- Serum suPAR levels depend on GFR
- Other groups were not able to reproduce suPAR-induced proteinuria in animal models
- Different suPAR isoforms are claimed to explain the above, but isoform-specific assays still do not exist
- Ultimate proof is still lacking: treatment of (recurrent) FSGS by specific removal of suPAR via immuno-adsorption

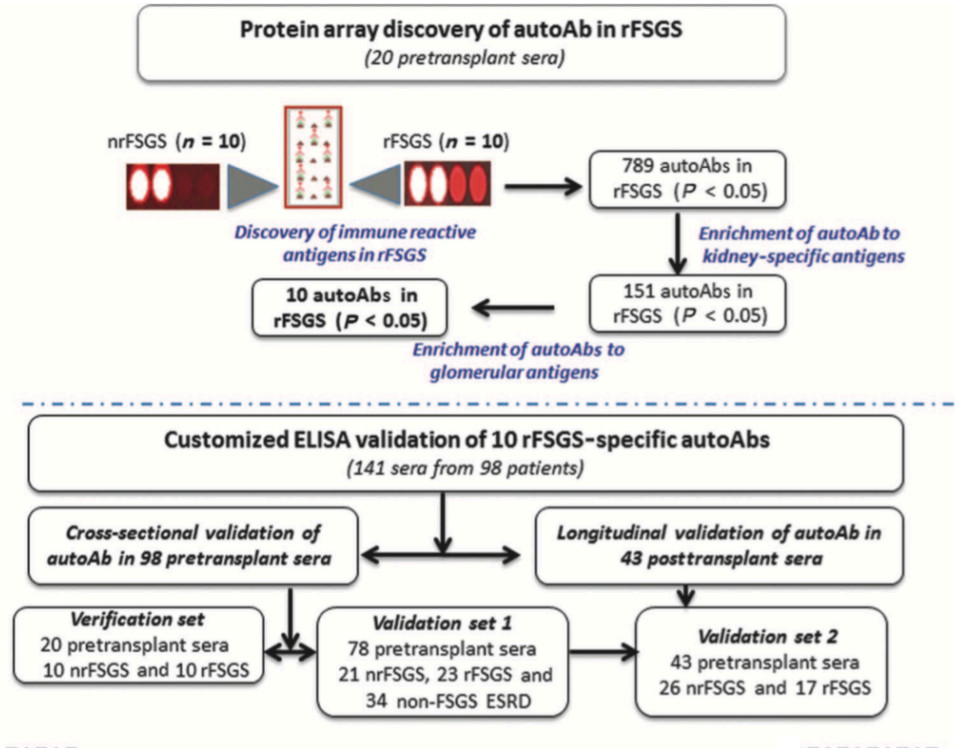
The NEW ENGLAND JOURNAL of MEDICINE

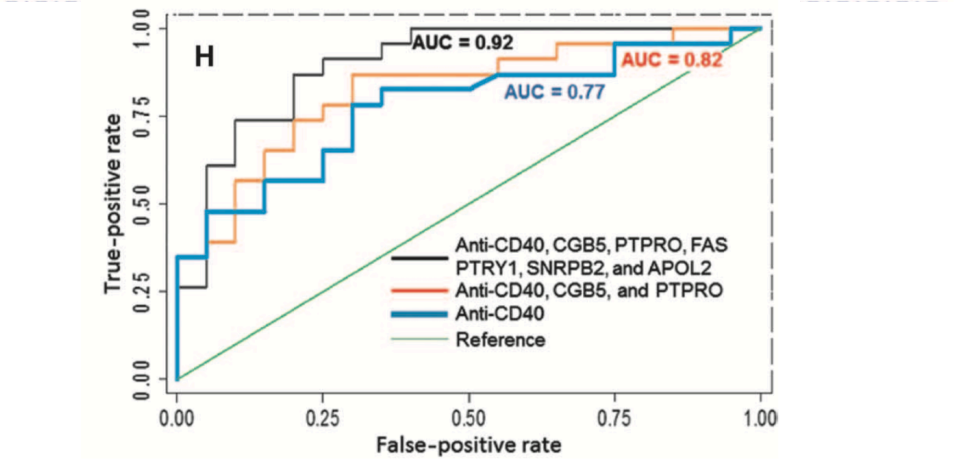
ORIGINAL ARTICLE

Soluble Urokinase Receptor and Chronic Kidney Disease

Salim S. Hayek, M.D., Sanja Sever, Ph.D., Yi-An Ko, Ph.D., Howard Trachtman, M.D., Mosaab Awad, M.D., Shikha Wadhwani, M.D., Mehmet M. Altintas, Ph.D., Changli Wei, M.D., Ph.D., Anna L. Hotton, Ph.D., M.P.H., Audrey L. French, M.D., Laurence S. Sperling, M.D., Stamatios Lerakis, M.D., Arshed A. Quyyumi, M.D., and Jochen Reiser, M.D., Ph.D.

Anti-CD40 autoantibodies





- Anti CD40-ab titers increased in FSGS patients with posttransplant recurrence (rFSGS) vs. Non-recurrent FSGS
- CD 40 expression was induced in glomeruli from rFSGS patients
- Anti-CD40 ab from rFSGS patients induced cytoskeletal changes in cultured podocytes and (very mild) proteinuria in mice
- Synergistic effect with suPAR

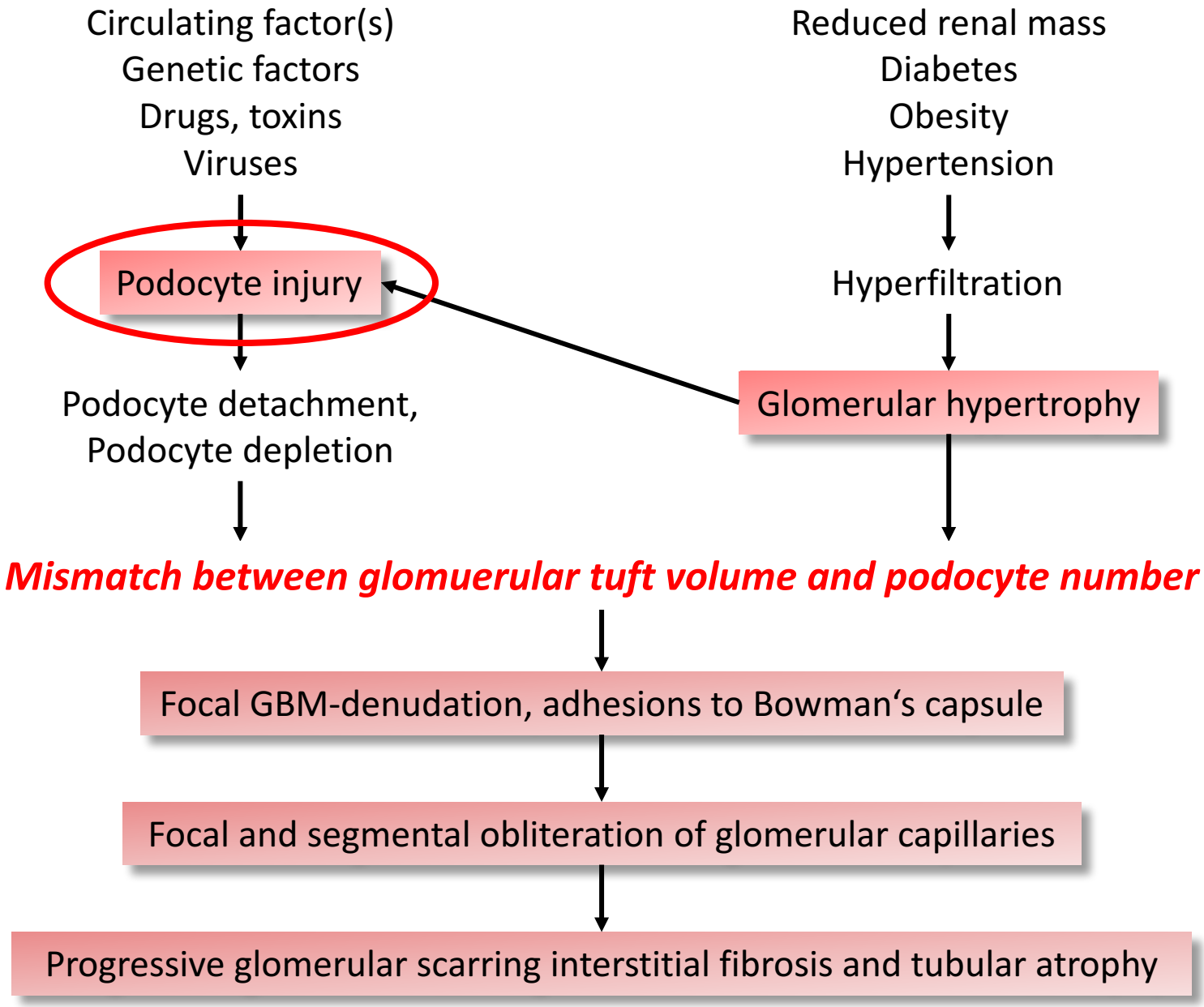
So…

… the jury is still out on the FSGS permeability factor!

Is there one circulating permeability factor that has just not yet been identified...

... or are there multiple permeability factors?

- *Each sufficient to cause FSGS (i.e. primary FSGS being a heterogenous disease)?*
- *Or is FSGS the consequence of multiple factors acting together?*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Focal GBM-denudation, adhesions to Bowman‘s capsule
Focal and segmental obliteration of glomerular capillaries
Progressive glomerular scarring interstitial fibrosis and tubular atrophy

The NEW ENGLAND JOURNAL of MEDICINE

BRIEF REPORT

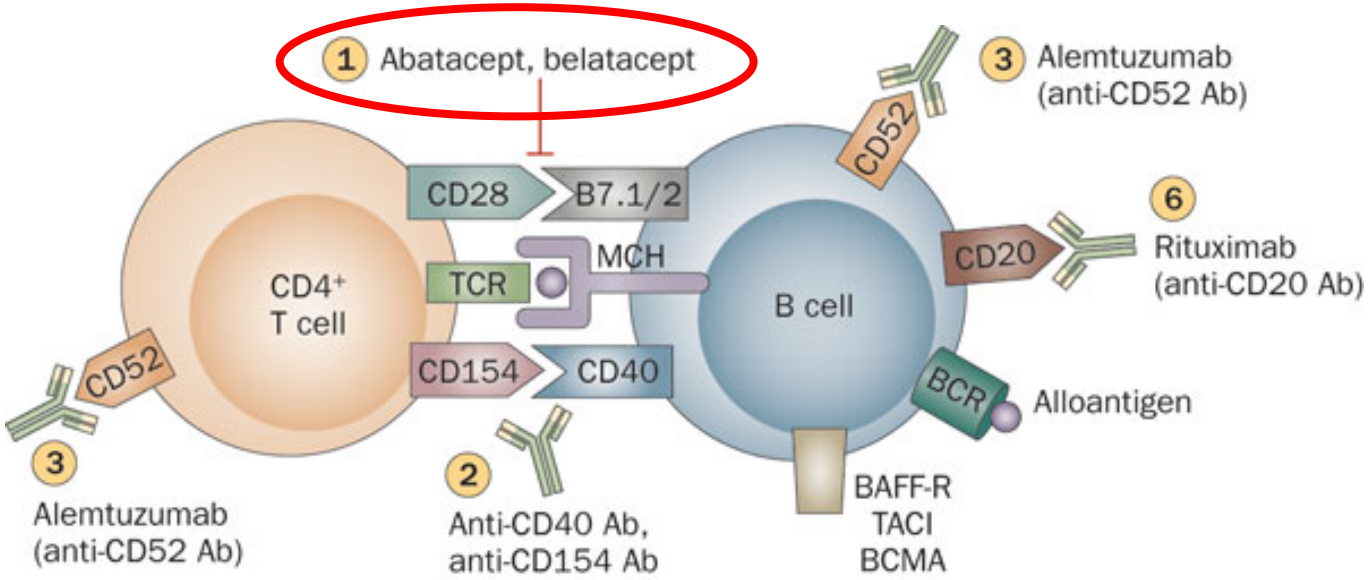
Abatacept in B7-1–Positive Proteinuric Kidney Disease

Chih-Chuan Yu, M.Sc., Alessia Fornoni, M.D., Ph.D., Astrid Weins, M.D., Ph.D., Samy Hakroush, M.D., Dony Maiguel, Ph.D., Junichiro Sageshima, M.D., Linda Chen, M.D., Gaetano Ciancio, M.D., Mohd. Hafeez Faridi, Ph.D., Daniel Behr, Kirk N. Campbell, M.D., Jer-Ming Chang, M.D., Hung-Chun Chen, M.D., Jun Oh, M.D., Christian Faul, Ph.D., M. Amin Arnaout, M.D., Paolo Fiorina, M.D., Ph.D., Vineet Gupta, Ph.D., Anna Greka, M.D., Ph.D., George W. Burke III, M.D., and Peter Mundel, M.D.

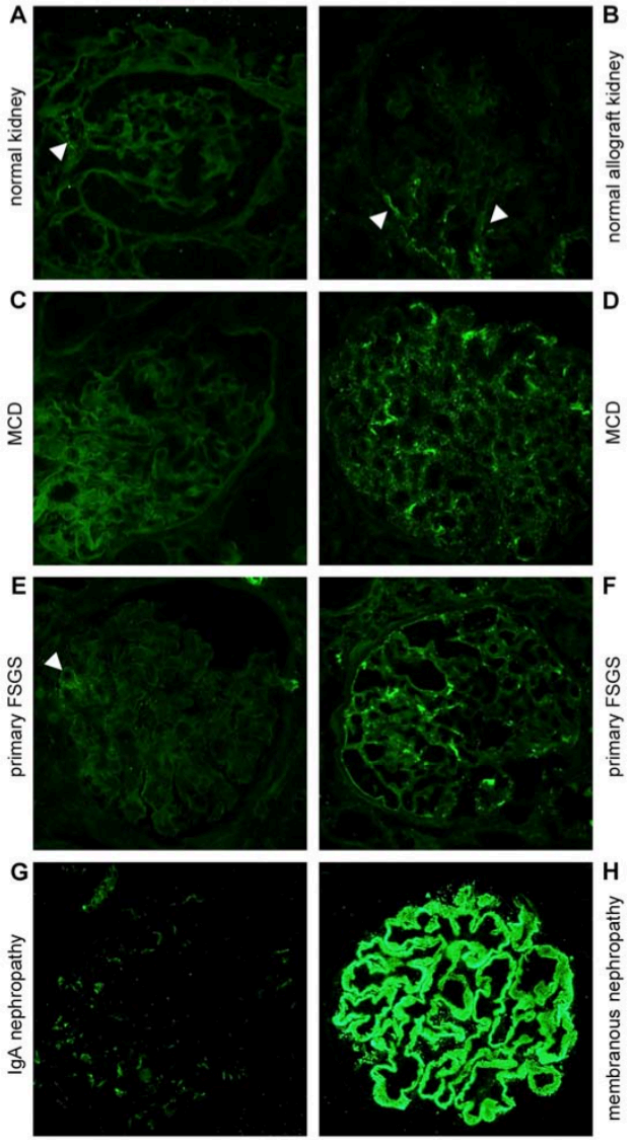
B7-1 (=CD80) and FSGS

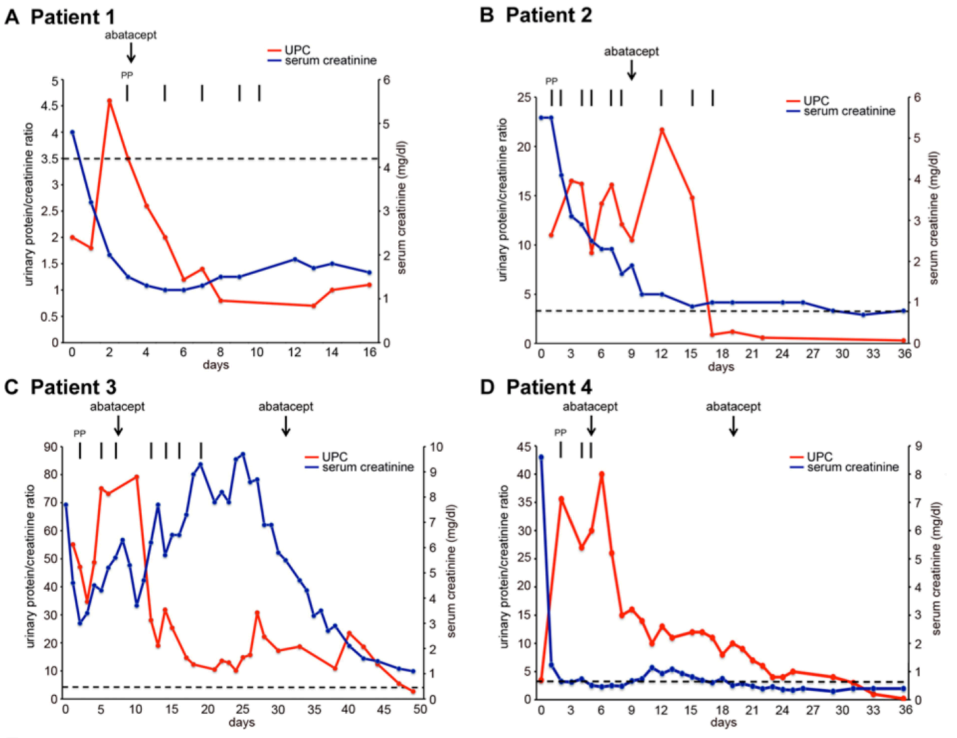
- B7-1 is a costimulatory molecule expressed on APCs
- B7-1 is expressed in podocytes in certain models of podocyte injury and in human glomerular diseases. Induction of B7-1-expression in podocytes by LPS-injection leads to proteinuria in mice.

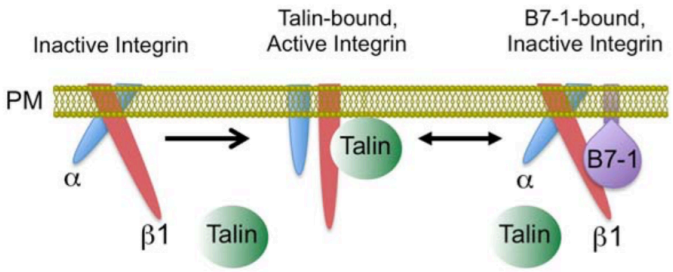
Reiser, JCI 2004;113:1390

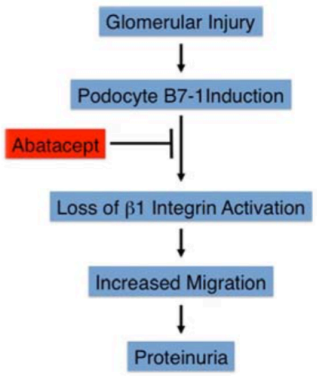


B7-1 (=CD80) and FSGS









Yu, NEJM 2013;19:369

Abatacept to treat FSGS?

- 5 cases, uncontrolled study, patients received multiple treatments (PEX...), clinical data not too convincing
- B7-1 staining in biopsy specimens unreliable (and not reproduced by other groups)
- B7-1 expression in podocytes (in several disease models and LPS-treated cultured podocytes) questioned

  Baye, Kidney Int 2016;90:1037
- Abatacept binds B7-1 on the extracellular domain, but the integrin - B7-1 interaction is intracellular
- Efficacy of abatacept and belatacept to reduce proteinuria not confirmed in several case reports and case series

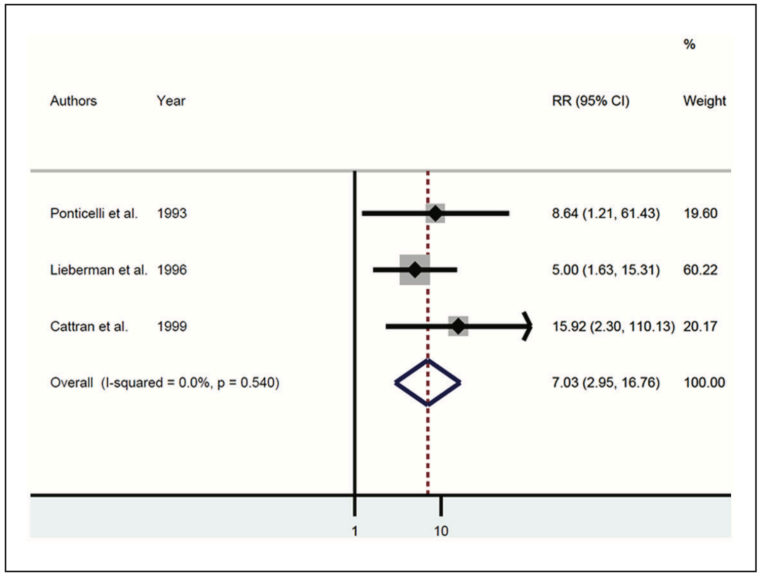
Treatment of FSGS 2017…

Steroids for treatment of primary FSGS

- No RCT has ever tested steroids vs. Placebo in FSGS
- Data are mostly from retrospective case series, including variable regmiens and durations
- Overall ca. 30-50% CR; 10-20% PR
- Response may take longer than in MCD (up to 16 weeks)

CNI for treatment of primary FSGS

- Indications: steroid resistance / frequent relapsing disease / initial treatment if steroids to be avoided
- 6 small RCT
  - 3 vs. placebo / supportive care
  - 3 vs. other immunosuppression
- Maximum treatment duration 6 months before tapering
- Primary endpoint CR / PR, short follow up
  - Ca. 70% vs. 15% CR+PR
  - But very high relapse rate after tapering
  - Only 1 study with longterm FU



Laurin 2017

MMF for treatment of primary FSGS

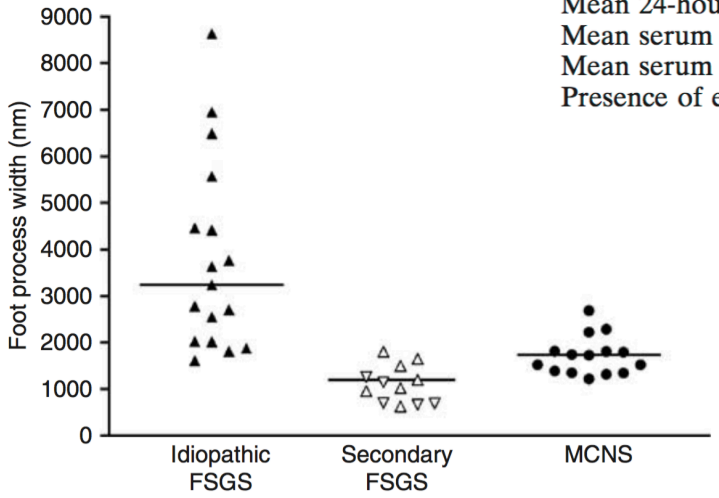
- Tested in 1 RCT in combination with dexamethasone vs. ciclosporine
  - n=138
  - Children and young adults, steroid resistant
  - Proteinuria >1g (decreased because of slow recruitment)
- No significant difference, but trend favoring ciclosporine and insufficient power
- + few other small studies (including various etiologies of SRNS)

Gipson, Kidney Int 2011;80:868

- ***Be aware that data are weak, studies have primarily included patients with NS and mostly refer to proteinuria remission as endpoint***
- ***Therefore, IS should generally be reserved to nephrotic patients***
- ***Make sure only to treat idiopathic FSGS with IS!***

Primary vs adaptive FSGS

Parameter	O-FSGS ($N = 57$)	I-FSGS ($N = 50$)	O-FSGS vs. I-FSGS (P value)
Mean S_{Cr} at biopsy *mg/dL*	1.55	1.96	0.903
Proteinuria			0.012
Non-nephrotic proteinuria *N* (%)	30 (52.6)	17 (34)	
Nephrotic range proteinuria *N* (%)	27 (47.4)	33 (66)	
Nephrotic parameters			
Nephrotic syndrome *N* (%)	4 (7)	27 (54)	<0.001
Mean 24-hour urine protein *g*	4.24	6.89	0.004
Mean serum albumin *g/dL*	3.8	2.9	<0.001
Mean serum cholesterol *mg/dL*	231.65	335.13	<0.001
Presence of edema *N* (%)	23 (40.4)	34 (68)	0.01



Presence of nephrotic syndrome

Kambham, Kidney Int 2001;59:1498

Clincal history

Degreee / extent of FP effacement

Deegens, Kidney Int 2008;74;1568

Some hints from the columbia classification

What I did not cover

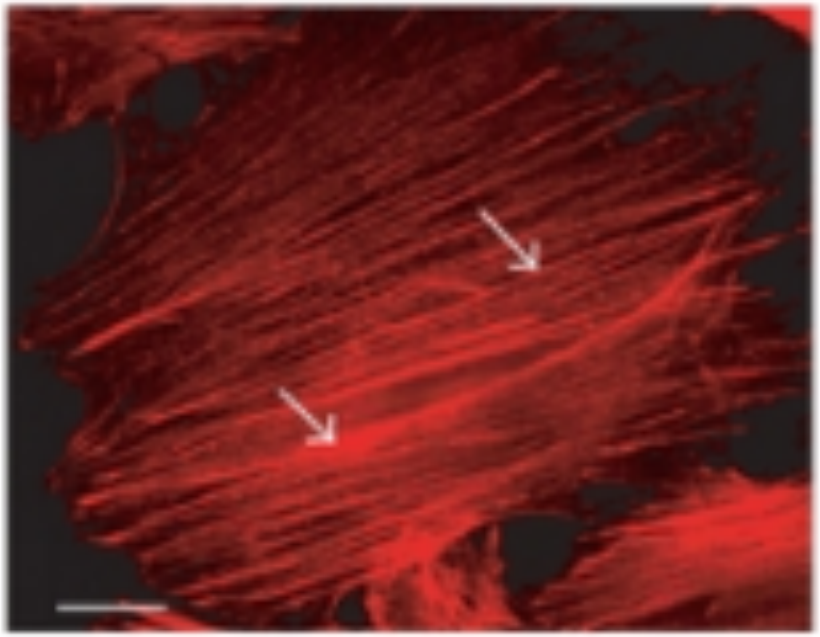
- FSGS vs. MCD
- Genetic forms of FSGS, when to perform genetic testing
- Histologic FSGS variants (Columbia classification)
- miRNA
- ...

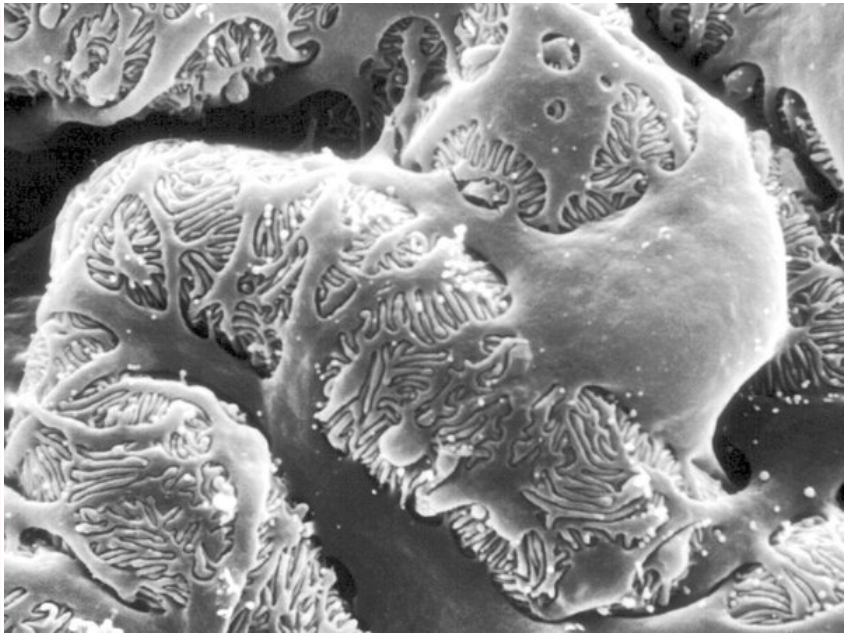
Conclusions

- FSGS is a histological lesion that can be caused by many different mechanisms leading to podocyte depletion and denuded GBM areas
- A circulating factor (or several factors) is likely involved in the pathogenesis of (at least some forms) of primary FSGS but the factor(s) has not yet been definitely identified

Conclusions

- Recent years have brought great advances in the understanding of podocyte biology - but unfortunately not yet led to novel treatments of FSGS





Conclusions

- Recent years have brought great advances in the understanding of podocyte biology - but unfortunately not yet led to novel treatments of FSGS
- Let‘s hope that effective, specific treatment options will finally become available, but don‘t make patients and yourself false hope based on experimental data and preliminary, uncontrolled clinical studies

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