Primary glomerulonephritides – selected news

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Simplified classification of primary glomerulonephritides

1. Nonproliferative - podocytopathies
   - minimal change disease
   - focal segmental glomerulosclerosis
   - membranous nephropathy
2. Proliferative -mesangiopathies
   - IgA nephropathy
   - membranoproliferative GN
3. *Diseases with endothelium as primary target*
   - *preeclampsia, HUS/TTP*
   - *type III and IV LN, AAV*

Selected topics

1. classification of podocyte injury – impact on outcome

2. genetic basis of podocyte injury – mutations and polymorphisms

3. molecular mechanisms of podocyte injury in MCD and FSGS

4. do we already have treatment with direct effect on podocyte?

5. news in the pathogenesis of IMN

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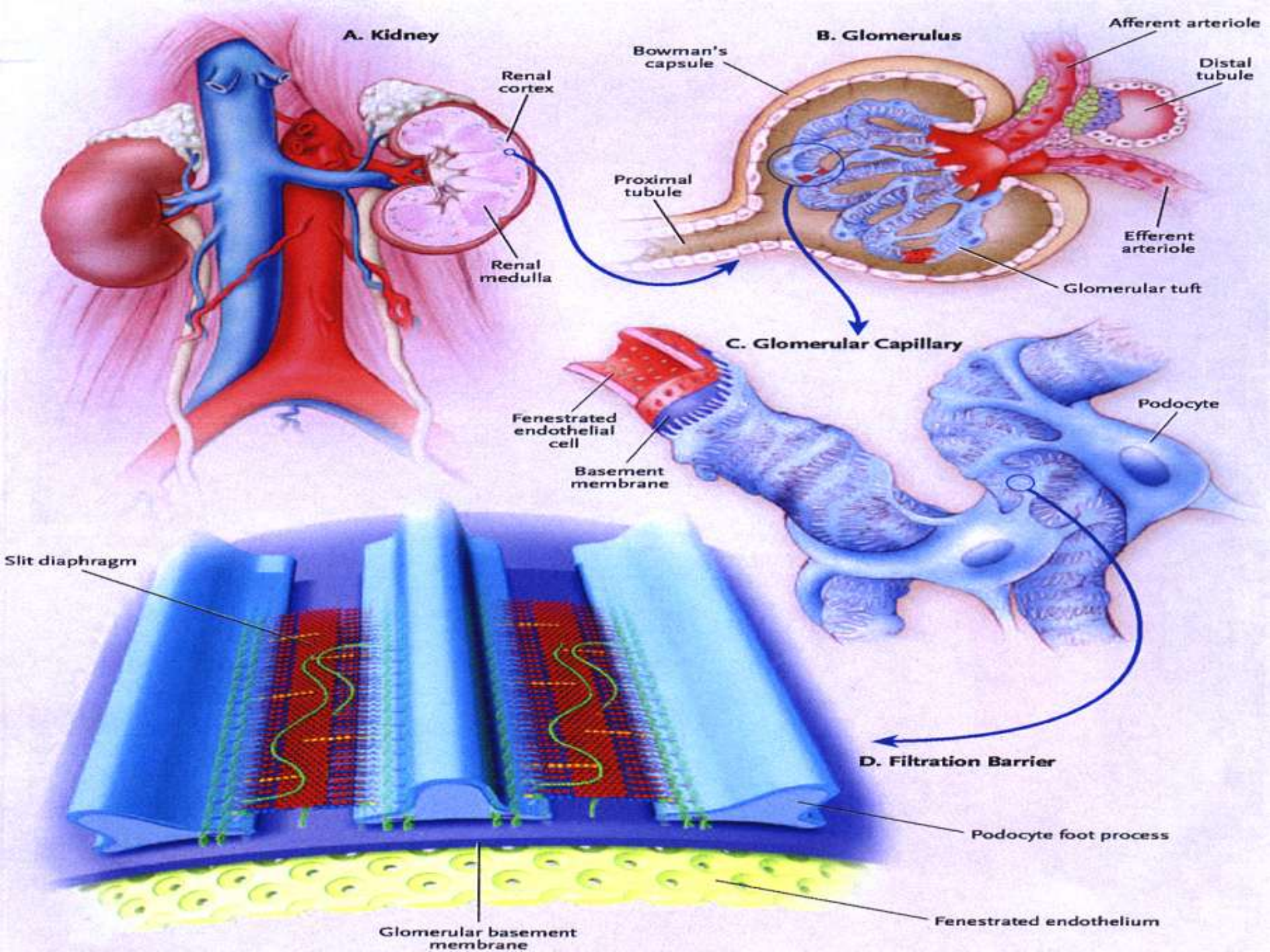
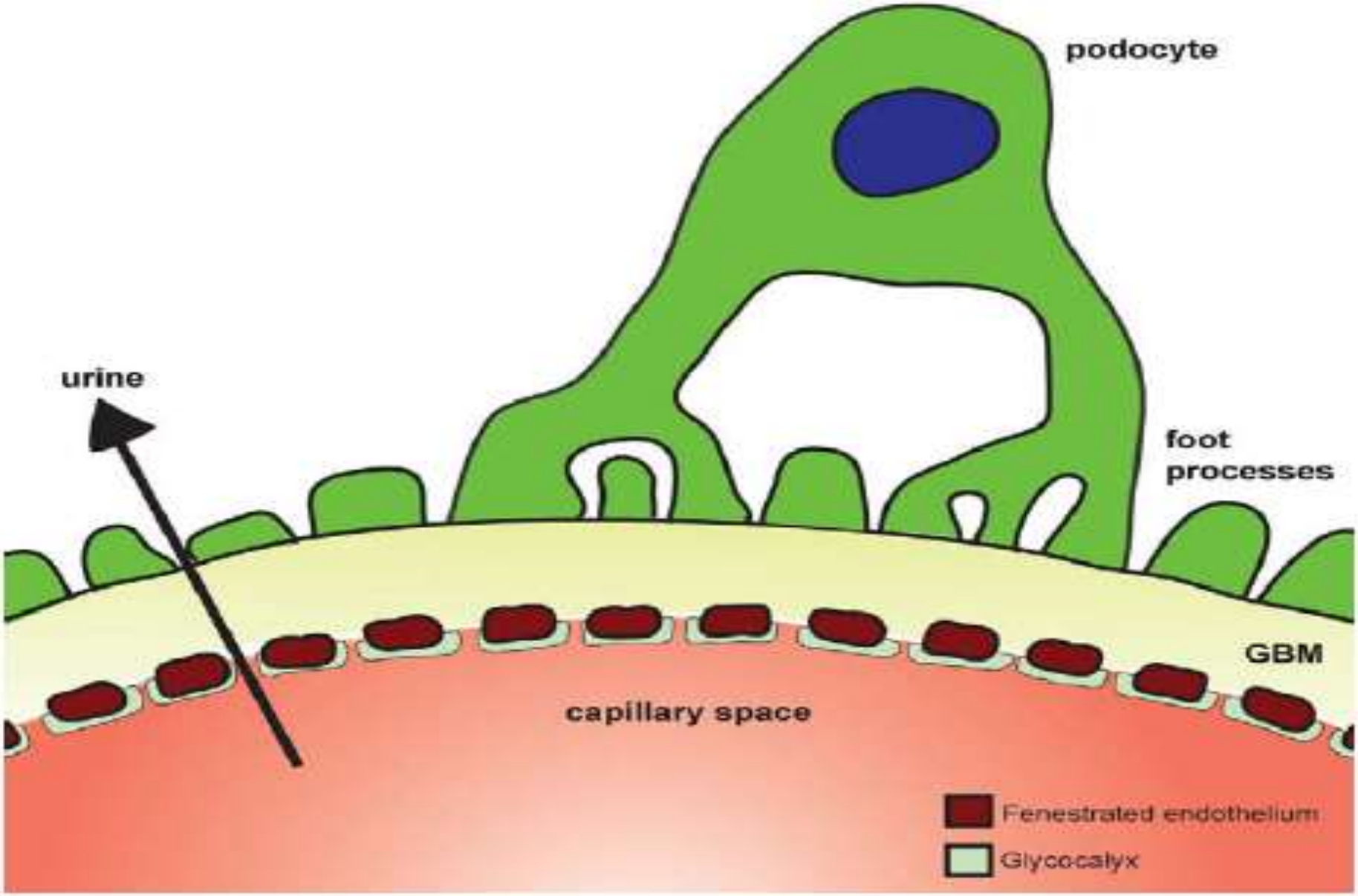

A. Kidney
Renal cortex
Renal medulla
B. Glomerulus
Bowman's capsule
Afferent arteriole
Distal tubule
Proximal tubule
Efferent arteriole
Glomerular tuft
C. Glomerular Capillary
Fenestrated endothelial cell
Basement membrane
Podocyte
Slit diaphragm
D. Filtration Barrier
Podocyte foot process
Fenestrated endothelium
Glomerular basement membrane

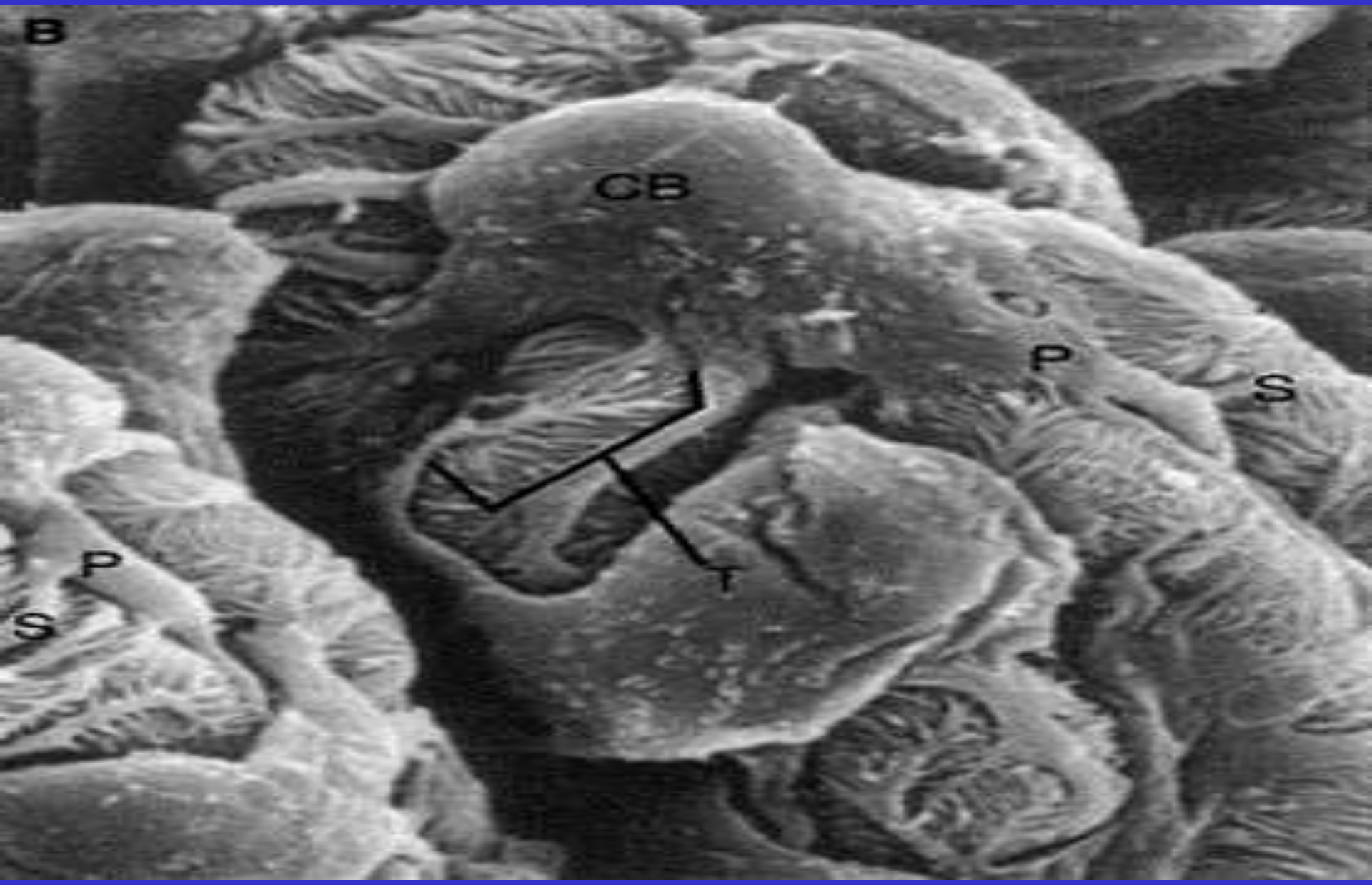
Molecular make-up of the glomerular filtration barrier

Jaakko Patrakka [a,b,*], Karl Tryggvason [a]

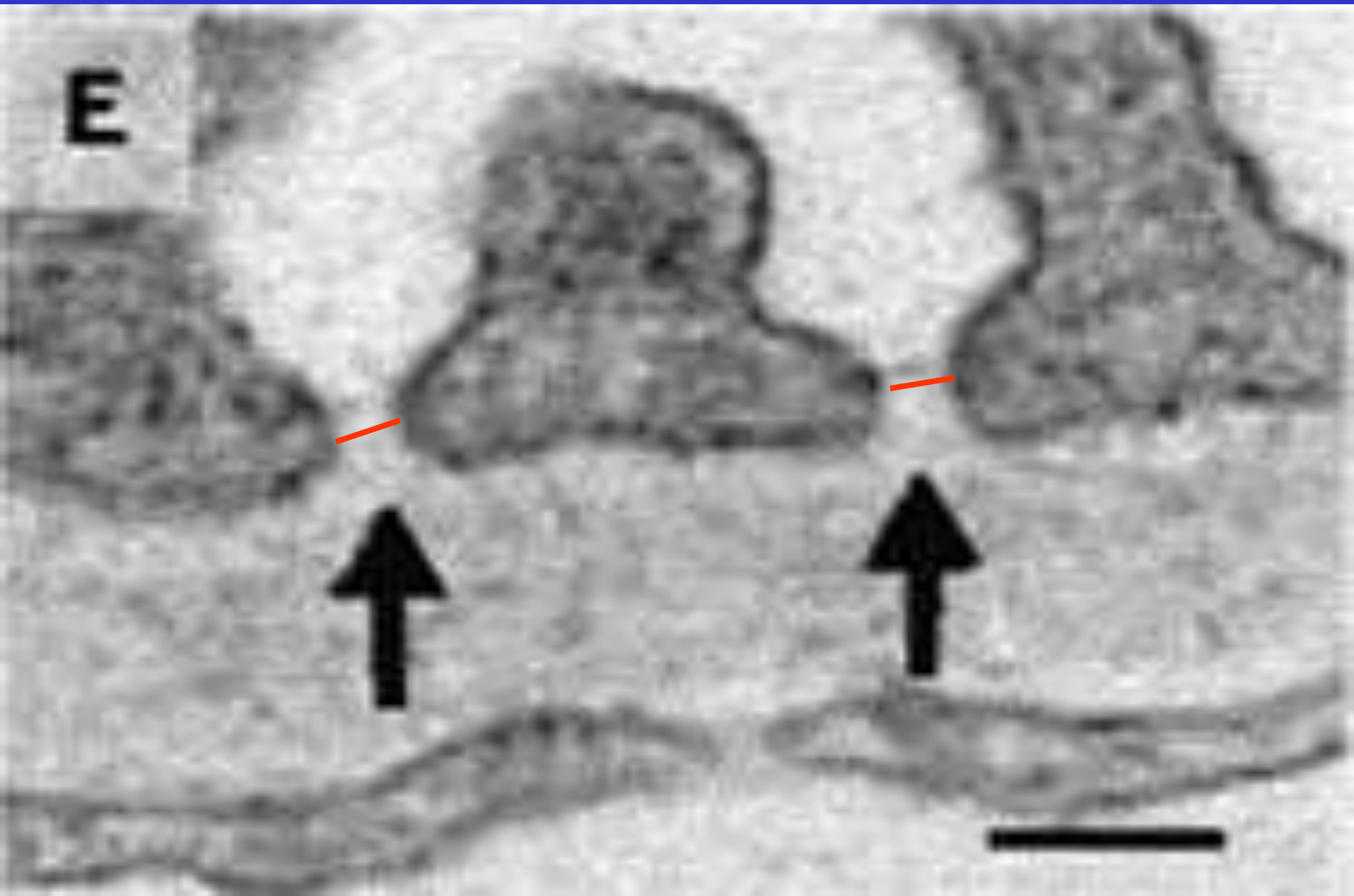
Biochemical and Biophysical Research Communications 396 (2010) 164–169



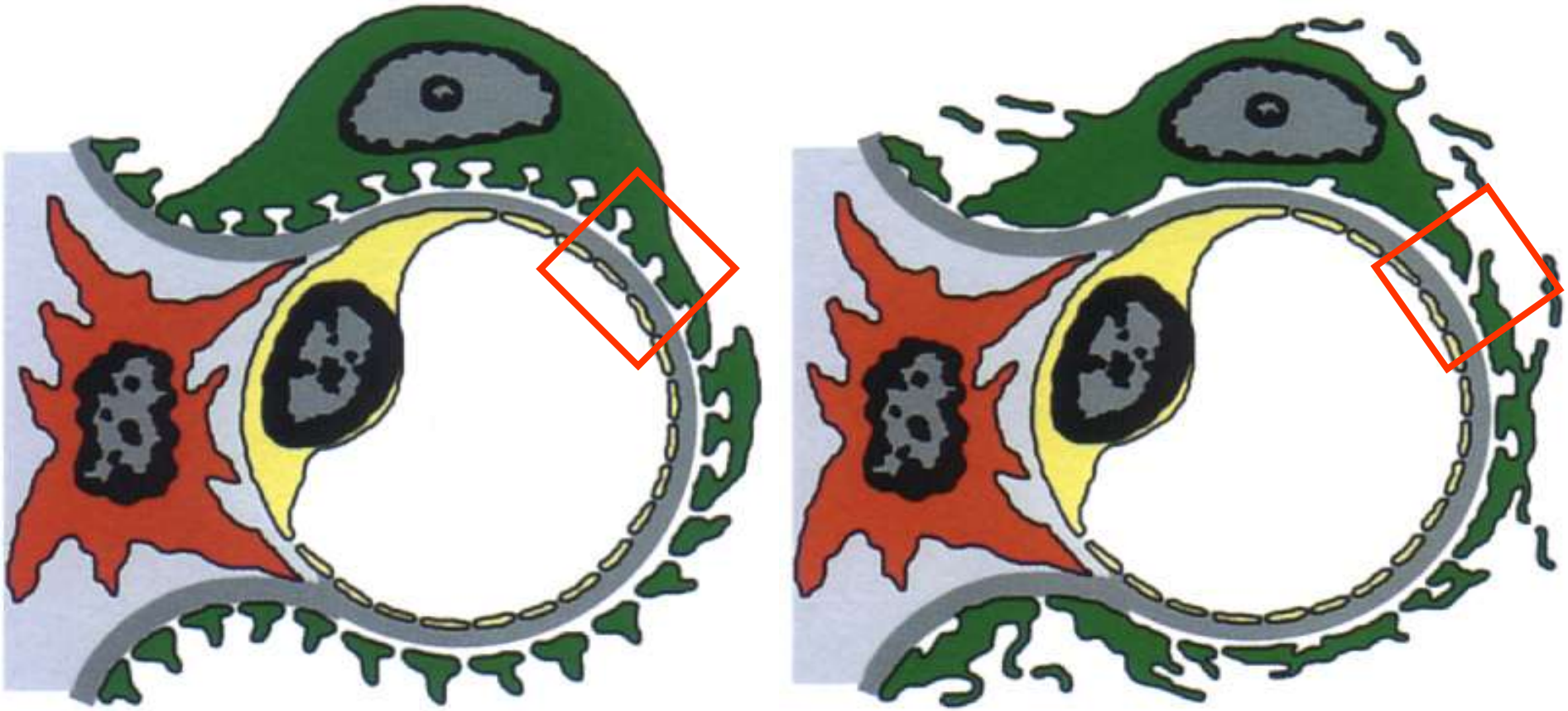
Podocyte foot processes



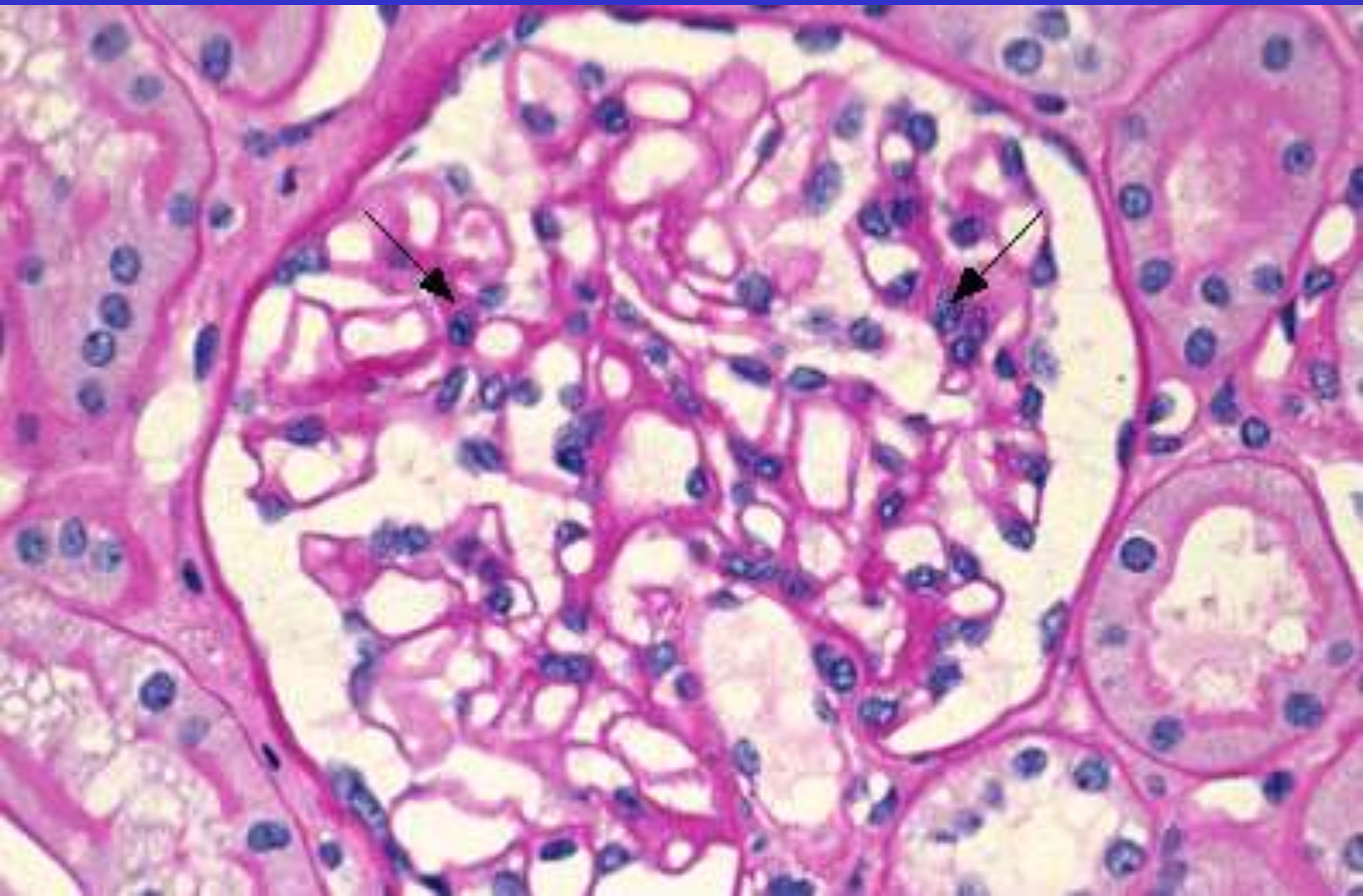
Slit diaphragm in normal GCW



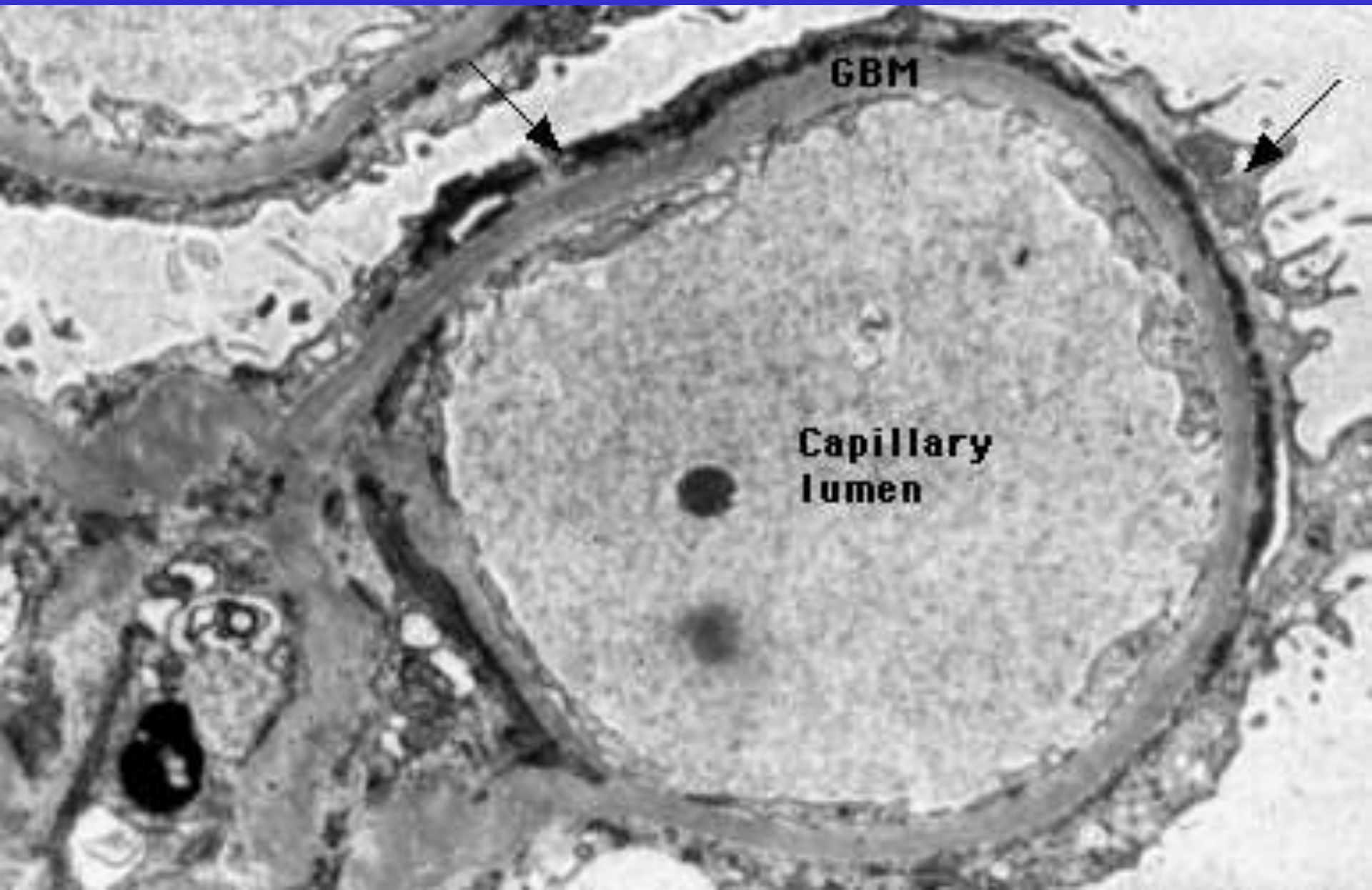
Minimal change disease



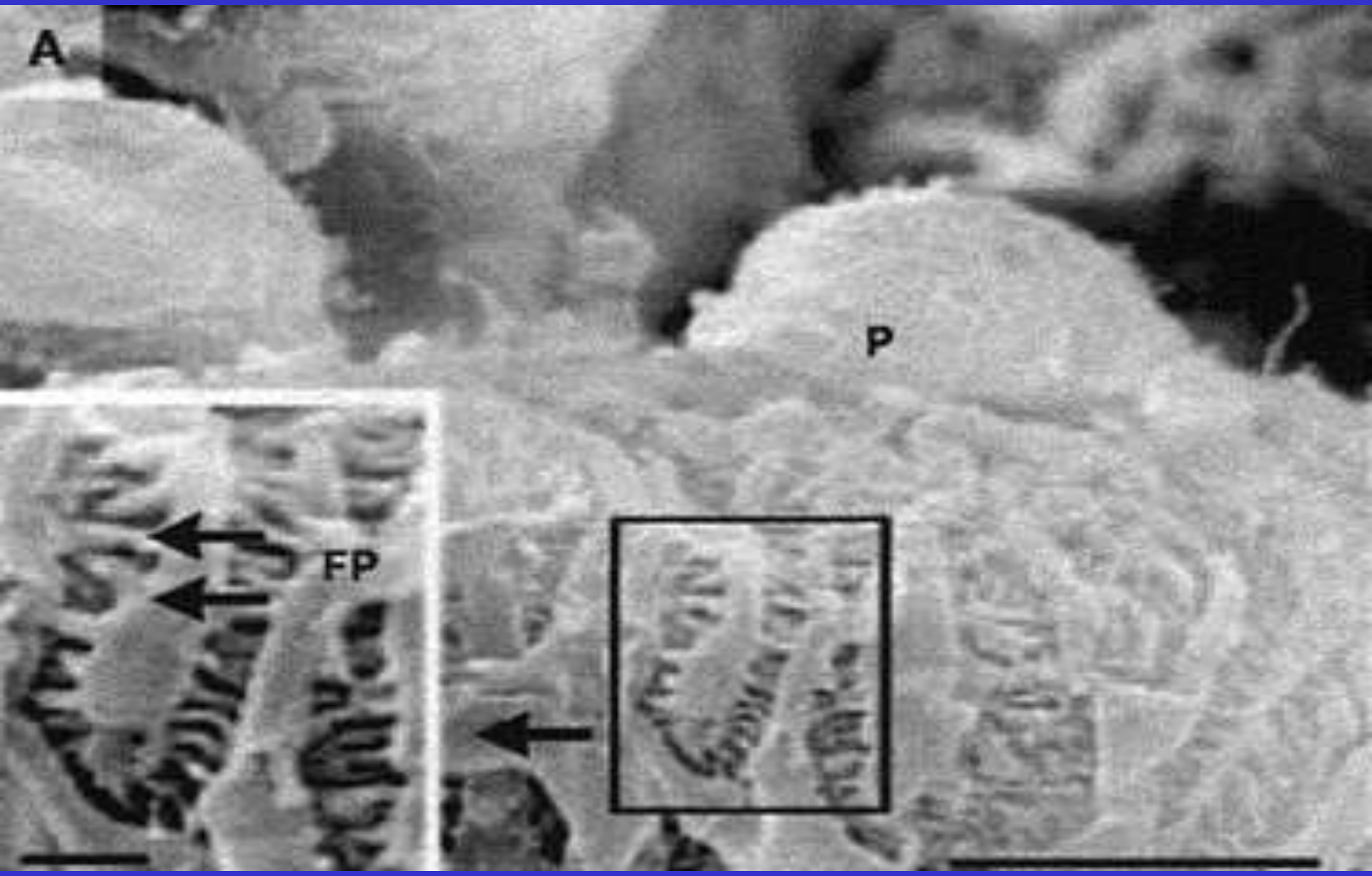
Minimal change disease



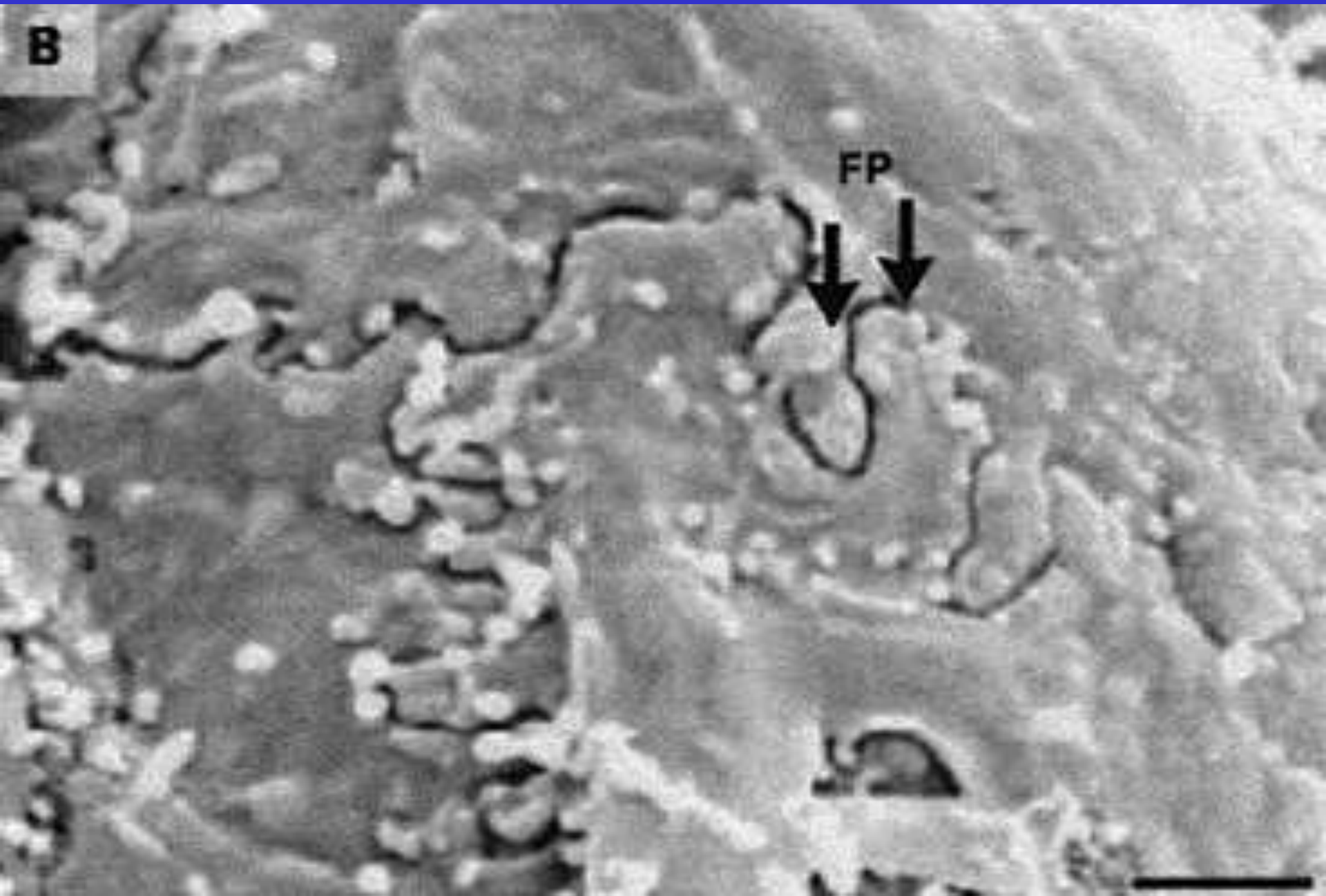
Minimal change disease



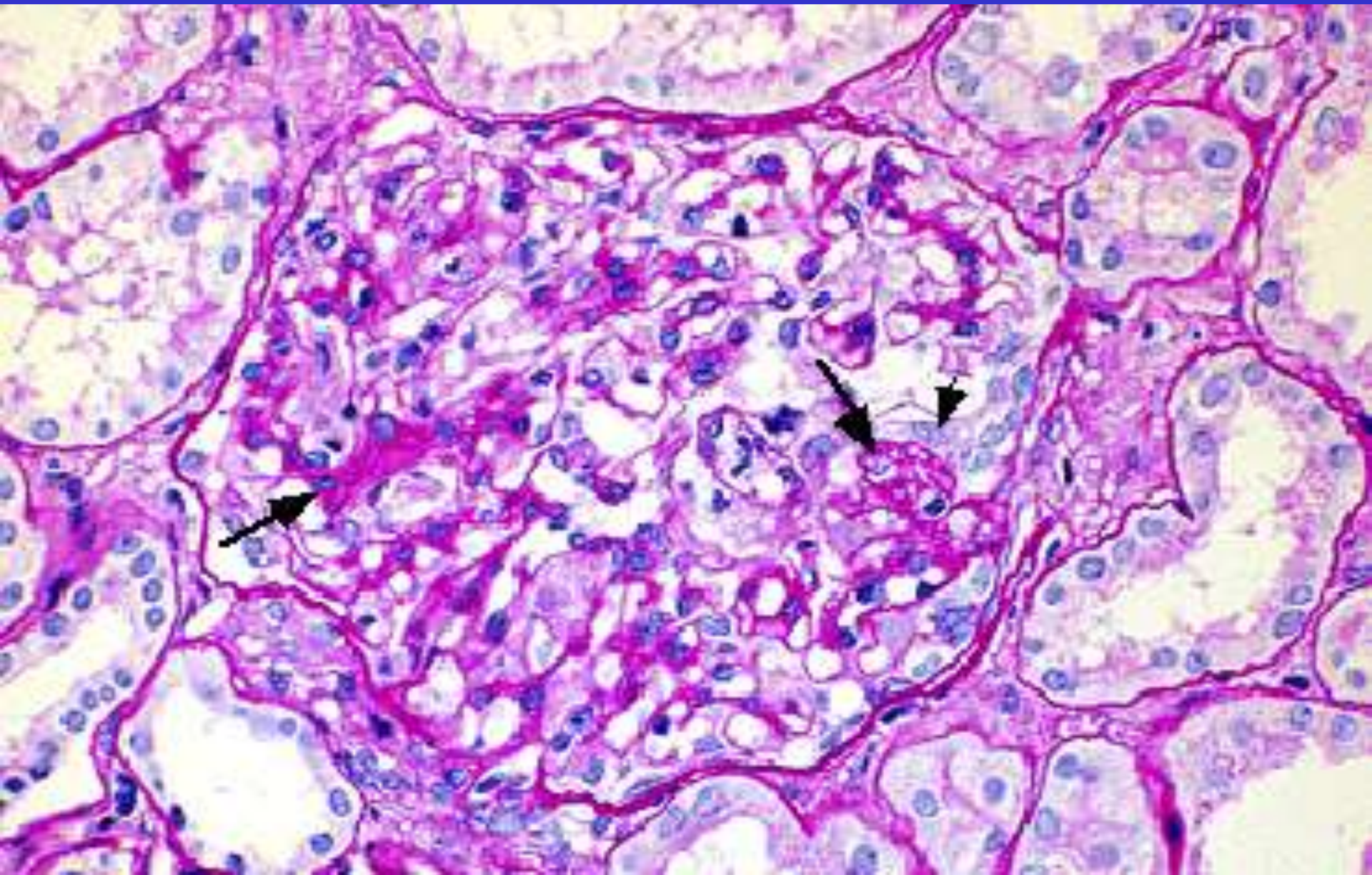
Podocytes in the healthy subject



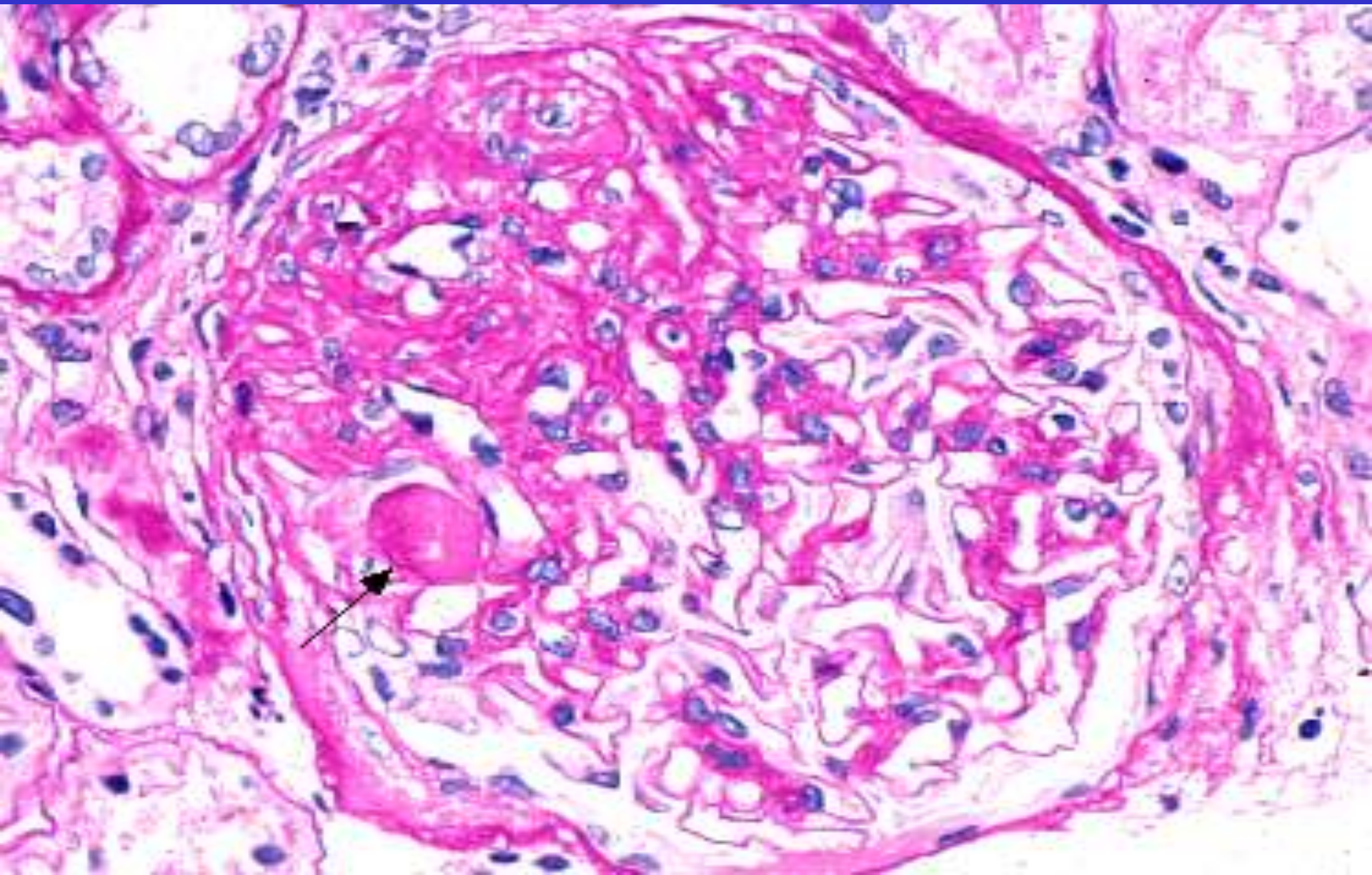
Podocytes in congenital nephrotic syndrome



Mild FSGS



Moderate FSGS

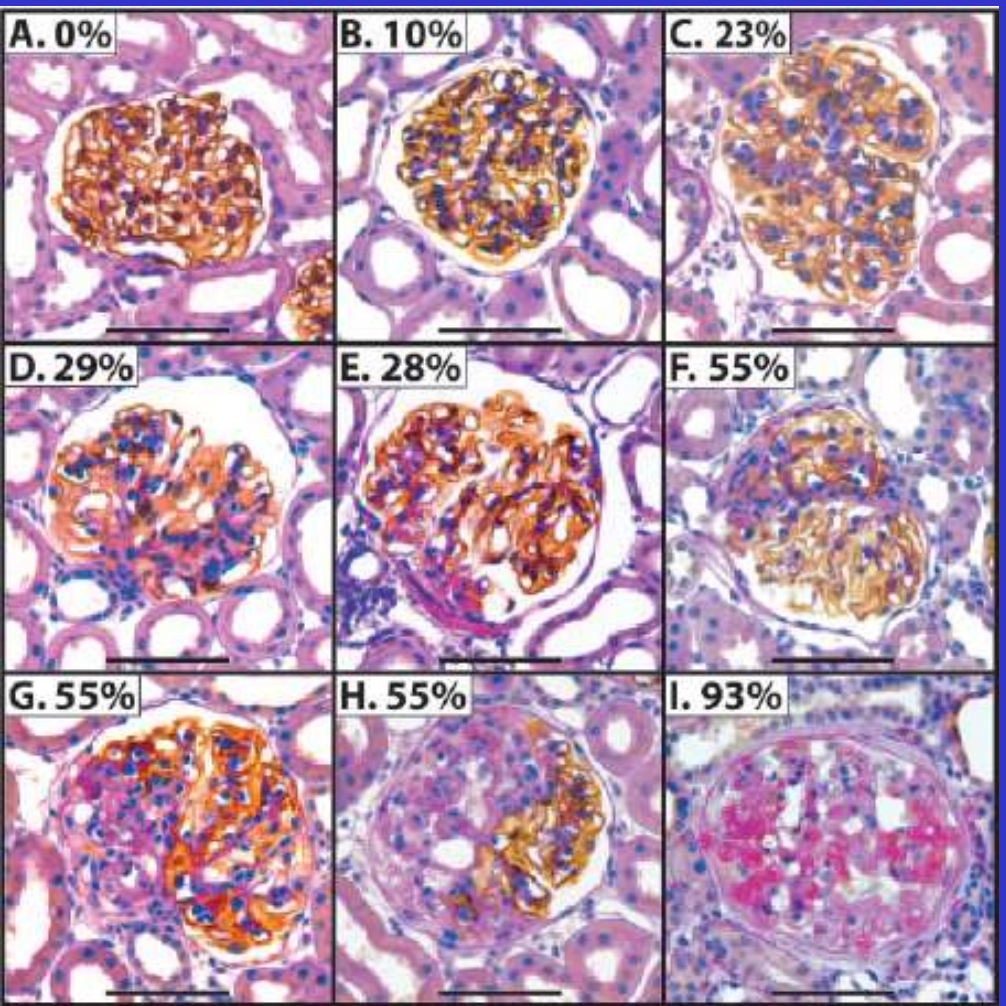


Podocyte Depletion Causes Glomerulosclerosis: Diphtheria Toxin–Induced Podocyte Depletion in Rats Expressing Human Diphtheria Toxin Receptor Transgene

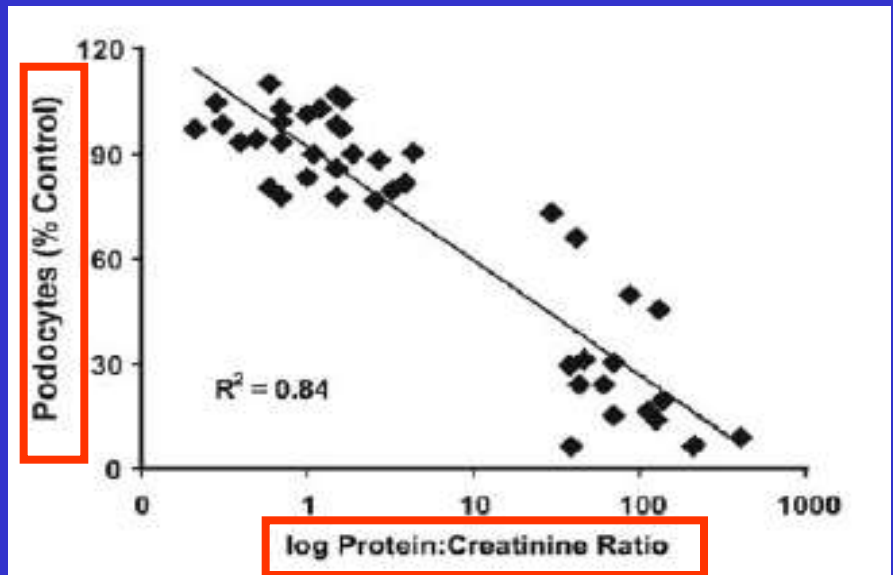
Bryan L. Wharram,* Meera Goyal,* Jocelyn E. Wiggins,† Silja K. Sanden,* Sabiha Hussain,* Wanda E. Filipiak,§ Thomas L. Saunders,‡§ Robert C. Dysko,‖ Kenji Kohno,¶ Lawrence B. Holzman,* and Roger C. Wiggins*

J Am Soc Nephrol 16: 2941–2952, 2005

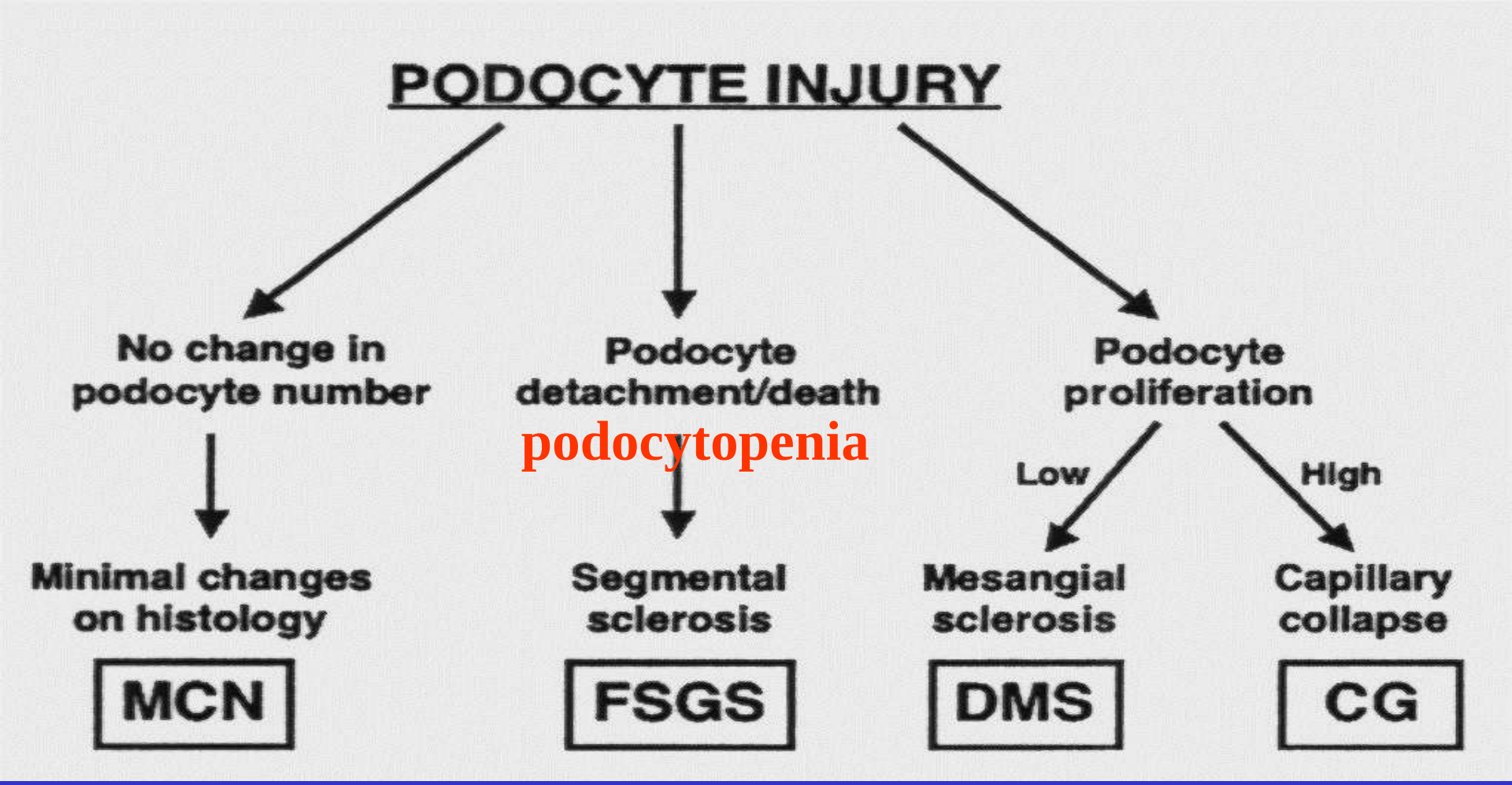
Graded podocyte depletion leads to:



1) transient proteinuria (0-20%)
2) mesangial expansion (20 – 40%) and focal sclerosis
3) progressive focal and then global glomerulosclerosis (> 40%)



Proposed taxonomy of the podocytopathies

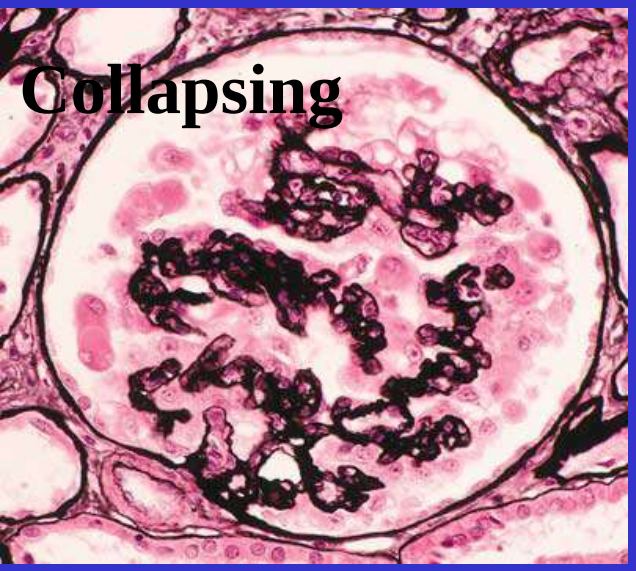


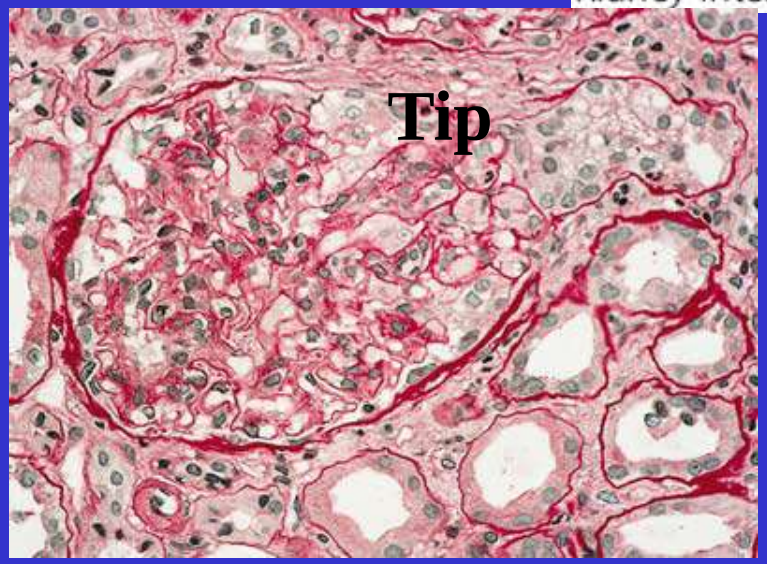
Barisoni et al., Clin. J. Am. Soc. Nephrol., 2007, 2: 529 - 542

Clinical and pathologic characteristics of focal segmental glomerulosclerosis pathologic variants

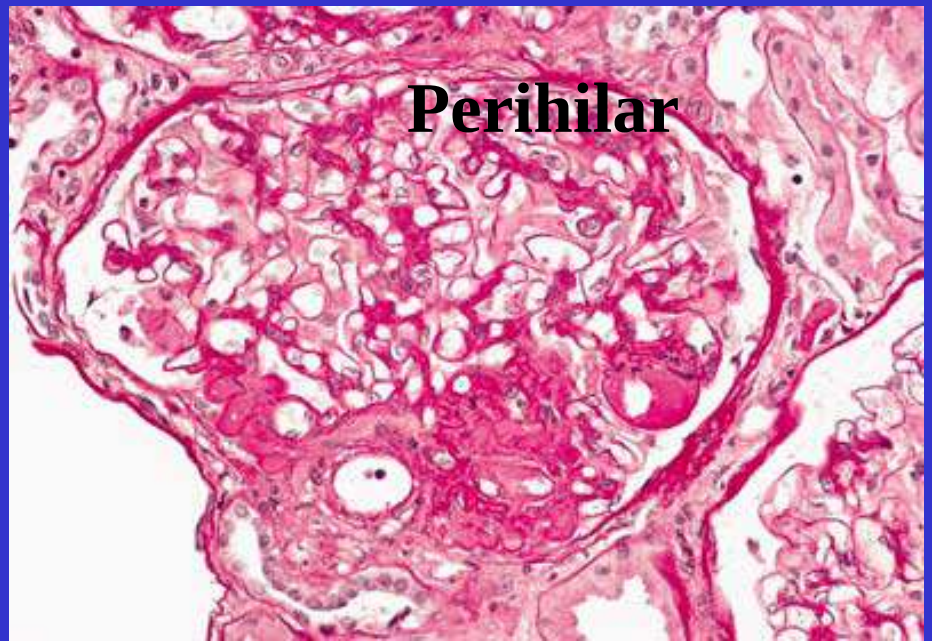
DB Thomas[1,3], N Franceschini[2,3,4], SL Hogan[2], S ten Holder[2], CE Jennette[2], RJ Falk[2] and JC Jennette[1]

Kidney International (2006) **69,** 920–926.





1. Collapsing
2. Cellular
3. Perihilar
4. Tip
5. Not otherwise defined



Clinical and pathologic characteristics of focal segmental glomerulosclerosis pathologic variants

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Kidney International (2006) **69,** 920–926.

Table 1 | Demographics, clinical presentation, and outcomes of focal segmental glomerulosclerosis variants

		Focal segmental glomerulosclerosis variants					
	Total cohort (*N*=197)	Cellular (*N*=6)	Collapsing (*N*=22)	Tip (*N*=34)	Perihilar (*N*=52)	NOS (*N*=83)	*P*-value
Age	49±15	45±13	38±12[a]	54±13	50±16	50±15	0.0009
(range)	(23-89)	(30-61)	(24-73)	(28-73)	(23-89)	(23-81)	
Male (%)	55	67	45	50	56	58	0.70
Black (%)	40	33	91[b]	15[b]	29	43	<0.001
Nephrotic syndrome (%)	70	75	83	88	55[c]	67	0.01
Hypertension (%)	74	75	67	54	80	80	0.05
MAP (mmHg)	107±14	110±10	106±13	111±16	105±14	107±13	0.30
Serum creatinine (mg/dl)	2.1±2.0	2.5±1.7	3.1±3.8	1.5±0.9[d]	2.0±1.4	2.1±1.8	0.02
Serum albumin (g/dl)	3.1±0.9	2.8±0.9	2.5±1.0[b]	2.5±0.9[b]	3.7±0.6	3.2±0.8	<0.0001
Cholesterol (mg/dl)	289±127	278±184	280±132	359±141	242±68	283±130	0.14
Proteinuria (g/day)	6.8±4.9	16±15	10.0±5.3[b]	9.7±7.0[b]	4.4±3.3	5.5±4.6	<0.001
Median (inter-quartile range)	5(3-9)	14 (7-26)	12 (4-15)	7(5-12)	4 (2-6)	5 (3-7)	
Complete remission[e] (%)	19	33	14	50[f]	10	13	<0.0001
Partial or complete remission[e] (%)	24	33	18	53[f]	19	16	<0.0001
1-year renal survival (%)	86	83	74	88	89	86	—[g]
3-year renal survival (%)	67	NA	33	76	75	65	—[g]

Clinical and pathologic characteristics of focal segmental glomerulosclerosis pathologic variants

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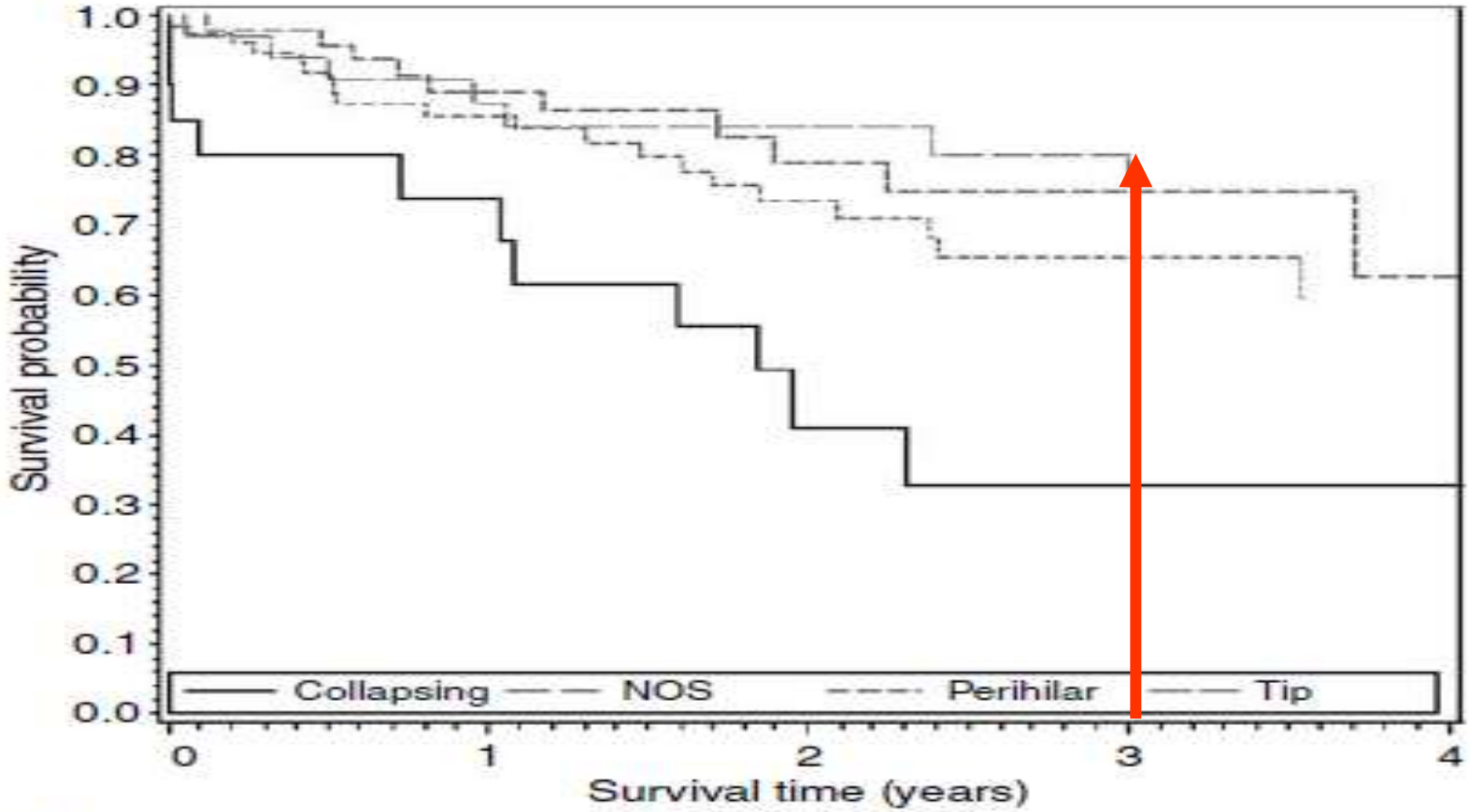
Kidney International (2006) **69,** 920–926.

Survival in different variants of FSGS



Patients at risk					
Collapsing	20	12	5	3	3
NOS	78	47	33	17	6
Perihilar	50	35	21	12	4
Tip	34	26	22	19	11

Selected topics

1. classification of podocyte injury – impact on outcome

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Etiology of FSGS

1. Secondary FSGS

   a. mutation of podocyte genes

   b. healing focal lesions (FSGN)

   c. hyperfiltration in residual nephrons

      - agenesis of one kidney
      - vesicoureteral reflux
      - morbid obesity

   d. damage to epithelial cells

      - HIV nephropathy
      - heroin nephropathy

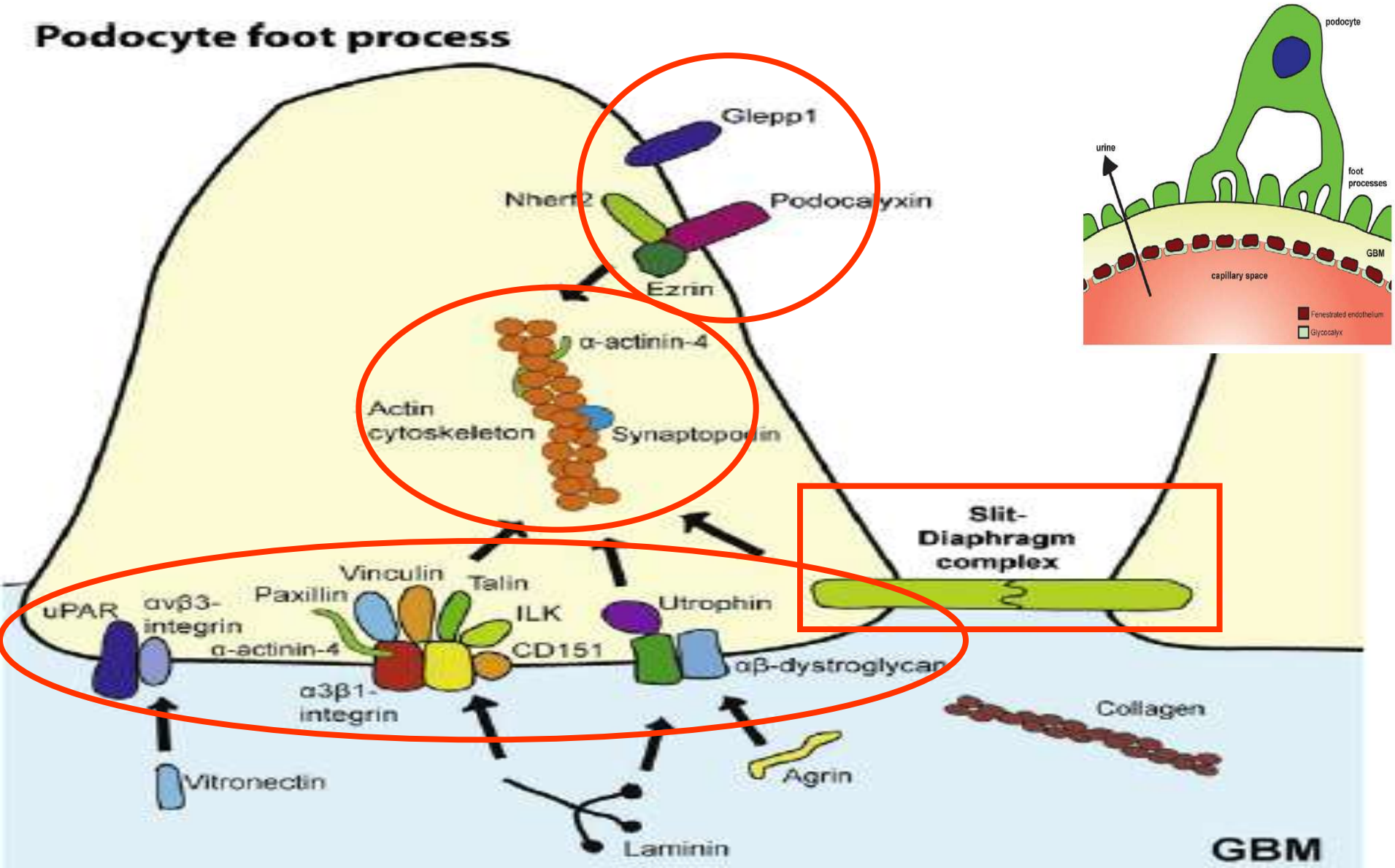
2. Primary (idiopathic) FSGS

   believed to be caused by circulating PF

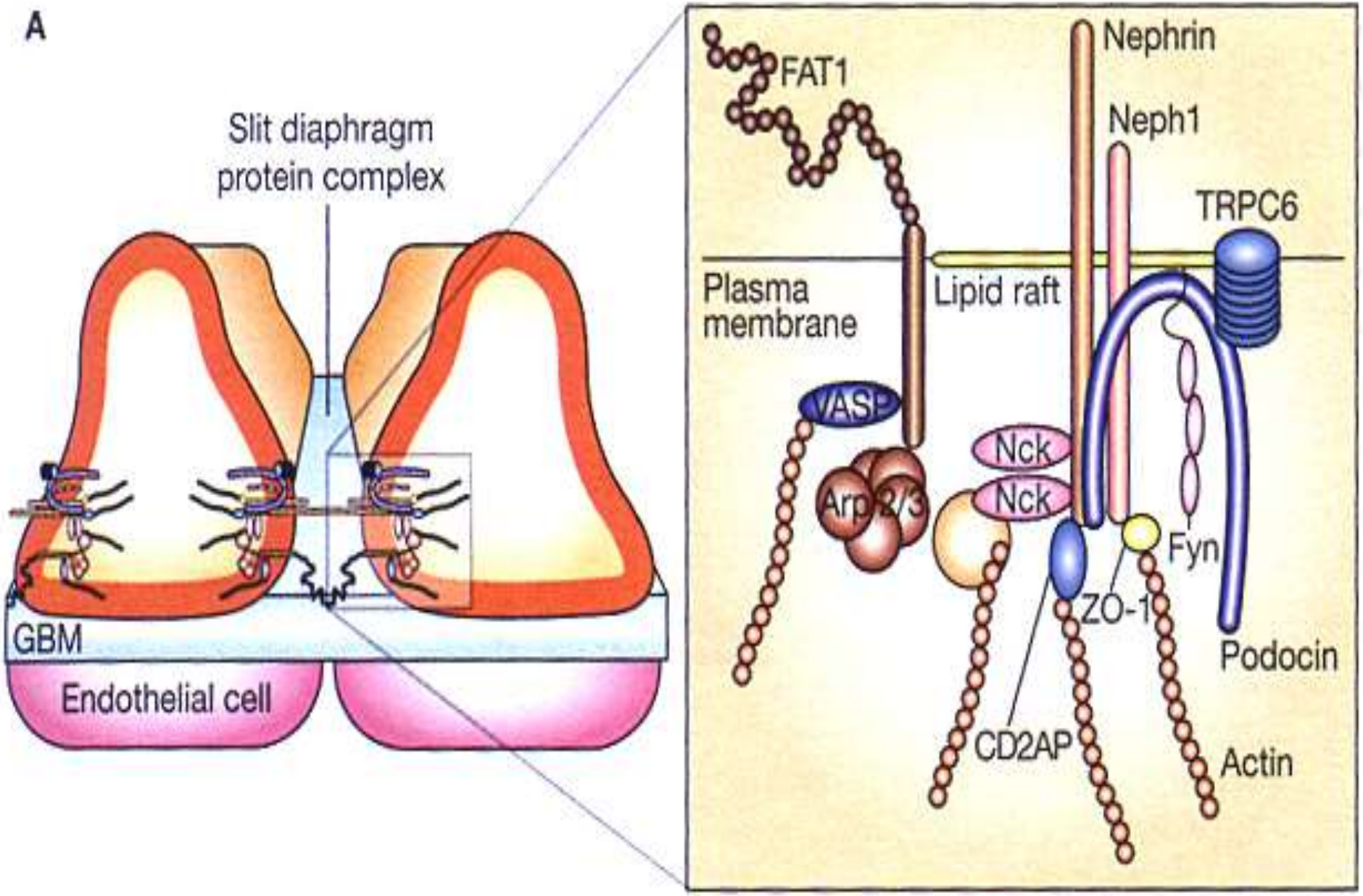
Molecular make-up of the glomerular filtration barrier

Jaakko Patrakka [a,b,*], Karl Tryggvason [a]

Biochemical and Biophysical Research Communications 396 (2010) 164–169



Lipid raft in the podocyte membrane



Identified nonsyndromic FSGS/NS genes

Disease	Locus	Inherit.	Gene	Protein
Congenital NS	19q13.1	AR	NPHS1	Nephrin
SRNS	1q25-32	AR	NPHS2	Podocin
FSGS1	19q13	AD	ACTN4	α-actinin
FSGS2	11q21-22	AD	FSGS2	TRPC6
FSGS3	6q	AD, AR	FSGS3	CD2AP
DMS	10q23.32-24.1	AR	NPHS3	PLCE1
SSNS1	2p	AR	SSNS1	unknown

MYH9 is associated with nondiabetic end-stage renal disease in African Americans

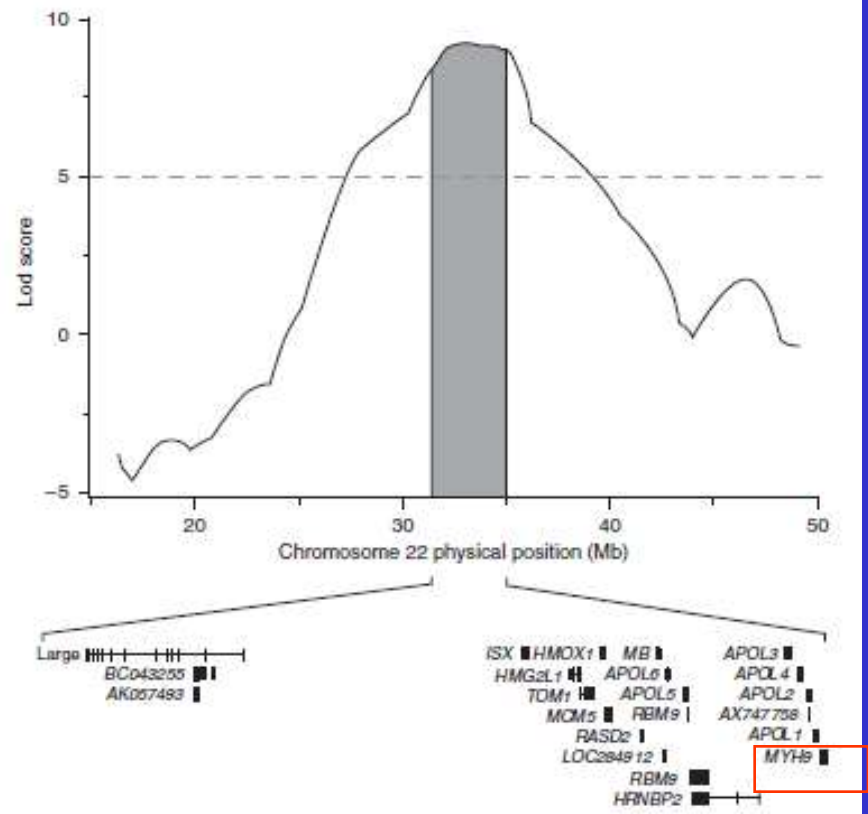
W H Linda Kao[1–3,25], Michael J Klag[1–3,25], Lucy A Meoni[2–4], David Reich[5,6], Yvette Berthier-Schaad[1], Man Li[1], Josef Coresh[1–4], Nick Patterson[6], Arti Tandon[5,6], Neil R Powe[1–3], Nancy E Fink[1–3], John H Sadler[7], Matthew R Weir[7], Hanna E Abboud[8], Sharon G Adler[9], Jasmin Divers[10], Sudha K Iyengar[11], Barry I Freedman[10], Paul L Kimmel[12], William C Knowler[13], Orly F Kohn[14], Kristopher Kramp[11], David J Leehey[15], Susanne B Nicholas[16], Madeleine V Pahl[17], Jeffrey R Schelling[18], John R Sedor[18,19], Denyse Thornley-Brown[20], Cheryl A Winkler[21], Michael W Smith[21,24] & Rulan S Parekh[1–3,22], on behalf of the Family Investigation of Nephropathy and Diabetes (FIND) Research Group[23]

nature genetics

October 2008

Table 1 Summary of results from admixture scans in African Americans with end-stage renal disease (ESRD)

ESRD phenotype	SNPs	Cases/Controls	Genome score	Lod score at chr. 22 peak
All ESRD	1,354	1,372/806	1.67	4.55
DM	1,351	703/806	0.47	–0.52
Non-DM	1,354	669/806	5.70[a]	8.56
HTN	1,352	347/806	–0.16	1.79
FSGS	1,350	87/806	0.10	2.47
GN	1,351	126/806	0.01	1.75
HIV	1,348	69/806	0.11	2.09



Polymorphisms in the non-muscle myosin heavy chain 9 gene (*MYH9*) are strongly associated with end-stage renal disease historically attributed to hypertension in African Americans

Barry I. Freedman[1], Pamela J. Hicks[2], Meredith A. Bostrom[2], Mary E. Cunningham[3], Yongmei Liu[3], Jasmin Divers[3], Jeffrey B. Kopp[4], Cheryl A. Winkler[5], George W. Nelson[5], Carl D. Langefeld[3] and Donald W. Bowden[1,2,6]

Kidney International (2009) **75,** 736–745

Polymorphisms in the Nonmuscle Myosin Heavy Chain 9 Gene (*MYH9*) Are Associated with Albuminuria in Hypertensive African Americans: The HyperGEN Study

Barry I. Freedman[a] Jeffrey B. Kopp[b] Cheryl A. Winkler[c] George W. Nelson[c] D.C. Rao[d] John H. Eckfeldt[e] Mark F. Leppert[f] Pamela J. Hicks[a] Jasmin Divers[a] Carl D. Langefeld[a] Steven C. Hunt[f]

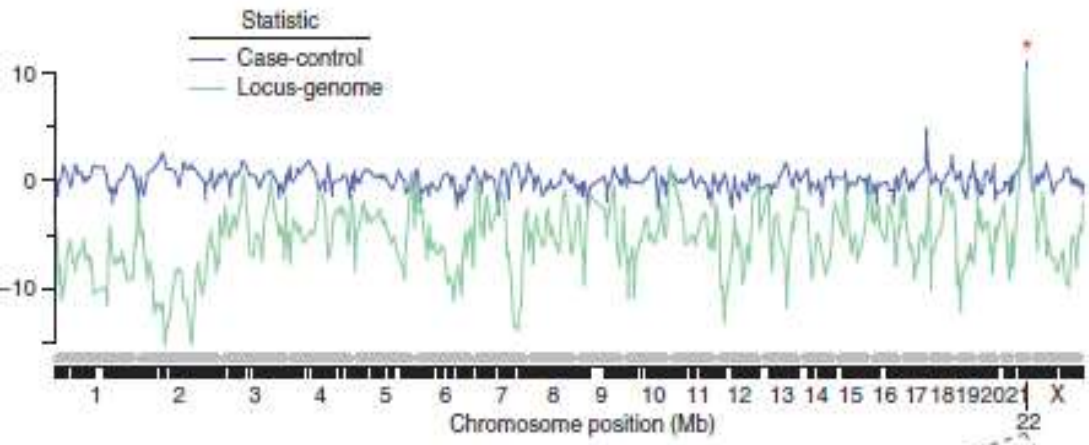
Am J Nephrol 2009;29:626–632

MYH9 is a major-effect risk gene for focal segmental glomerulosclerosis

Jeffrey B Kopp[1,17], Michael W Smith[2,16,17], George W Nelson[2,17], Randall C Johnson[2], Barry I Freedman[3], Donald W Bowden[3], Taras Oleksyk[2], Louise M McKenzie[2], Hiroshi Kajiyama[1], Tejinder S Ahuja[4], Jeffrey S Berns[5], William Briggs[6], Monique E Cho[1], Richard A Dart[7], Paul L Kimmel[8], Stephen M Korbet[9], Donna M Michel[10], Michele H Mokrzycki[11], Jeffrey R Schelling[12], Eric Simon[13], Howard Trachtman[14], David Vlahov[15] & Cheryl A Winkler[2]

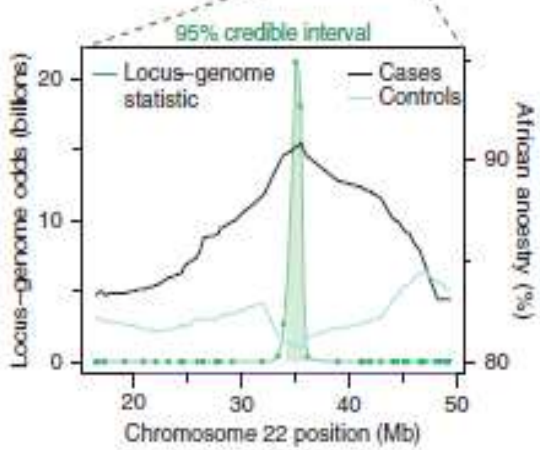
nature genetics

October 2008



Locus-genome lod score

	Genome-wide	Peak
Initial screen	9.2	12.4
Even markers	8.7	10.1
Odd markers	7.7	8.8
Dense markers at peak	10.5	13.7



Should be MYH9 polymorphisms tested in (African American) patients with FSGS before any immunosuppressive treatment?

Missense mutations in the *APOL1* gene are highly associated with end stage kidney disease risk previously attributed to the *MYH9* gene

Hum Genet Received: 7 June 2010 / Accepted: 6 July 2010
DOI 10.1007/s00439-010-0861-0

Shay Tzur · Saharon Rosset · Revital Shemer · Guennady Yudkovsky · Sara Selig · Ayele Tarekegn · Endashaw Bekele · Neil Bradman · Walter G. Wasser · Doron M. Behar · Karl Skorecki

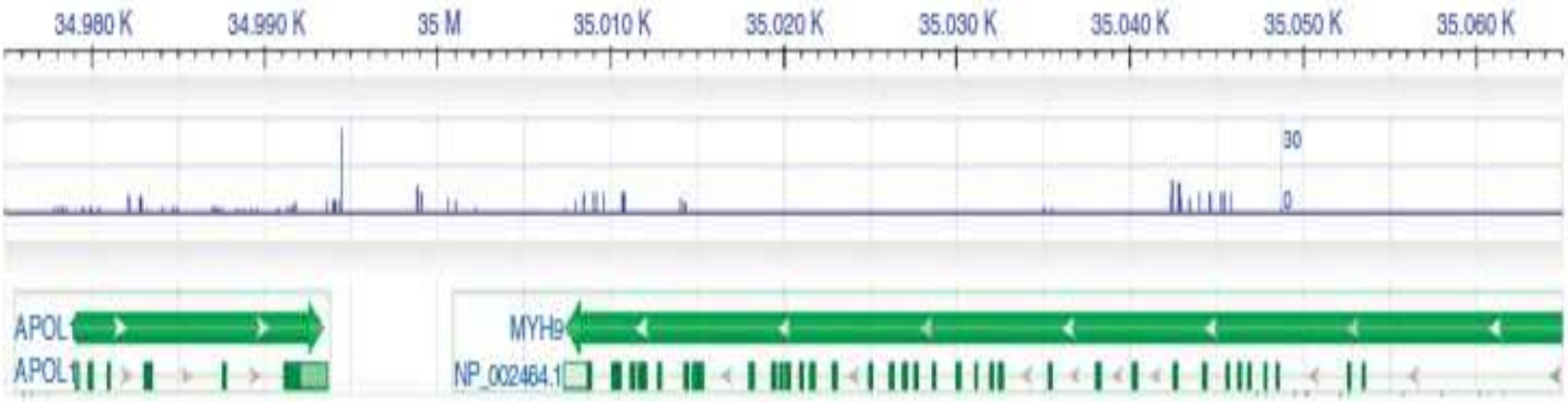
Abstract *MYH9* has been proposed as a major genetic risk locus for a spectrum of nondiabetic end stage kidney disease (ESKD). We use recently released sequences from the 1000 Genomes Project to identify two western African-specific missense mutations (S342G and I384M) in the neighboring *APOL1* gene, and demonstrate that these are more strongly associated with ESKD than previously reported *MYH9* variants. The *APOL1* gene product, apolipoprotein L-1, has been studied for its roles in trypanosomal lysis, autophagic cell death, lipid metabolism, as well as vascular and other biological activities. We also show that the distribution of these newly identified *APOL1* risk variants in African populations is consistent with the pattern of African ancestry ESKD risk previously attributed to *MYH9*.

A risk allele for focal segmental glomerulosclerosis in African Americans is located within a region containing APOL1 and MYH9

Kidney International advance online publication, 28 July 2010;

Giulio Genovese[1,2], Stephen J. Tonna[1,3], Andrea U. Knob[1], Gerald B. Appel[4], Avi Katz[5], Andrea J. Bernhardy[1], Alexander W. Needham[1], Ross Lazarus[6] and Martin R. Pollak[1,7]

A risk allele for FSGS in African Americans may be related not to MYH9, but to APOL1 which is related to Trypanosoma brucei infection

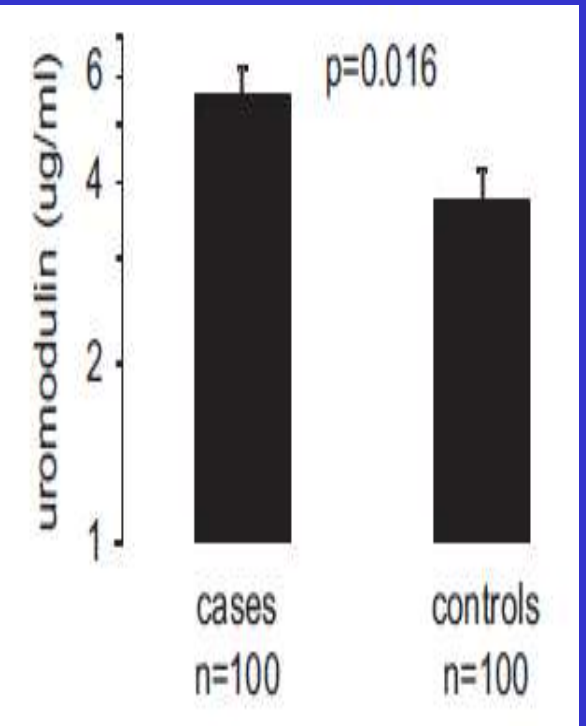


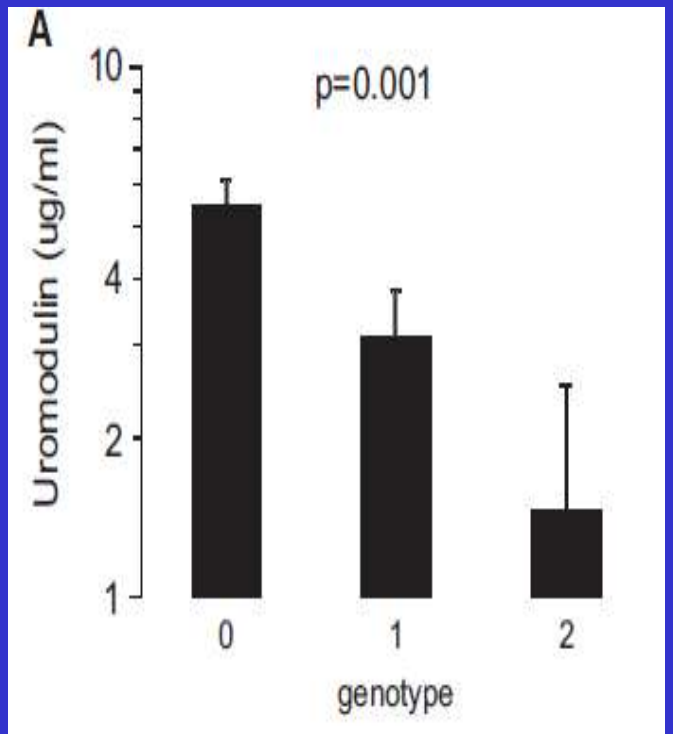
Uromodulin Levels Associate with a Common *UMOD* Variant and Risk for Incident CKD

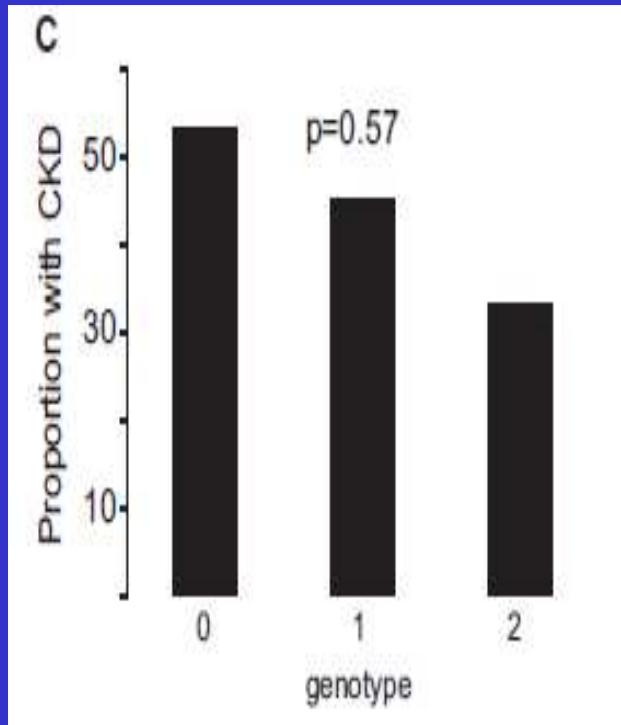
J Am Soc Nephrol 21: 337–344, 2010

Anna Köttgen,* Shih-Jen Hwang,†‡ Martin G. Larson,§ Jennifer E. Van Eyk,‖ Qin Fu,‖ Emelia J. Benjamin,†¶ Abbas Dehghan,** Nicole L. Glazer,†† W.H. Linda Kao,* Tamara B. Harris,‡‡ Vilmundur Gudnason,§§‖‖ Michael G. Shlipak,¶¶ Qiong Yang,§ Josef Coresh,* Daniel Levy,†‡ and Caroline S. Fox†‡***

Caucasian pts from FHS and ARIC studies with higher UMOD levels (determined genetically) had higher risk of lower GFR at 9 yr FU







Selected topics

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2. genetic basis of podocyte injury – mutations and polymorphisms

3. molecular mechanisms of podocyte injury in MCD and FSGS

4. do we already have treatment with direct effect on podocyte?

5. news in the pathogenesis of IMN

Plasma "Factors" in Recurrent Nephrotic Syndrome After Kidney Transplantation: Causes or Consequences of Glomerular Injury?

American Journal of Kidney Diseases, Vol 54, No 3 (September), 2009: pp 406-409

Box 1. Evidence for Circulating Factor in Recurrent Idiopathic Nephrotic Syndrome/Focal Segmental Glomerulosclerosis

- Immediate recurrence of proteinuria after transplantation[1,2]
- Transfer of proteinuria to fetus/infant[13]
- Efficacy of plasmapheresis, immunoadsorption in reducing proteinuria[3-5]
- Transfer of proteinuria to rat after injection of serum or plasma[6,7]
- Transfer of proteinuria to mice by patient stem cells[14]
- Increased glomerular permeability after incubation with serum or plasma[8-10]
- Progressive purification by sequential precipitation or affinity chromatography[15,16]
- Proteinuria after injection of active fractions[7,15]
- Identification of unique substances in plasma of affected patients; selected as candidates based on mechanistic hypotheses or discovered by using proteomics
- Substances without documented permeability activity[17-21]
- Substances that cause proteinuria or increase glomerular permeability[22,23]

Soluble ST2 protein

Cardiotrophin-like cytokine 1

Soluble urokinase receptor

Minireview

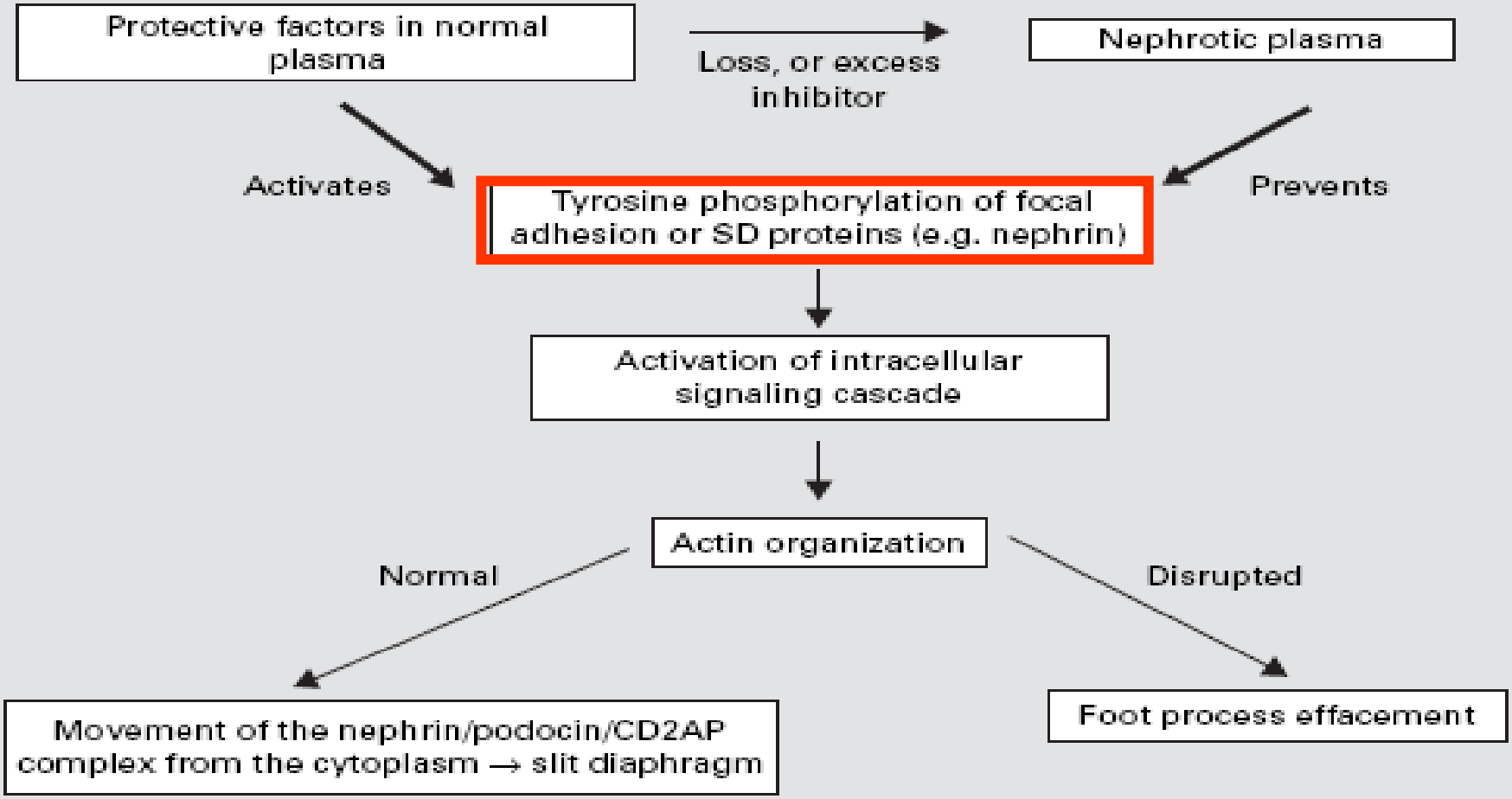
nephron Experimental Nephrology

Nephron Exp Nephrol 2006;104:e1–e5
DOI: 10.1159/000093259

Published online: May 11, 2006

The Bioactivity of Plasma Factors in Focal Segmental Glomerulosclerosis

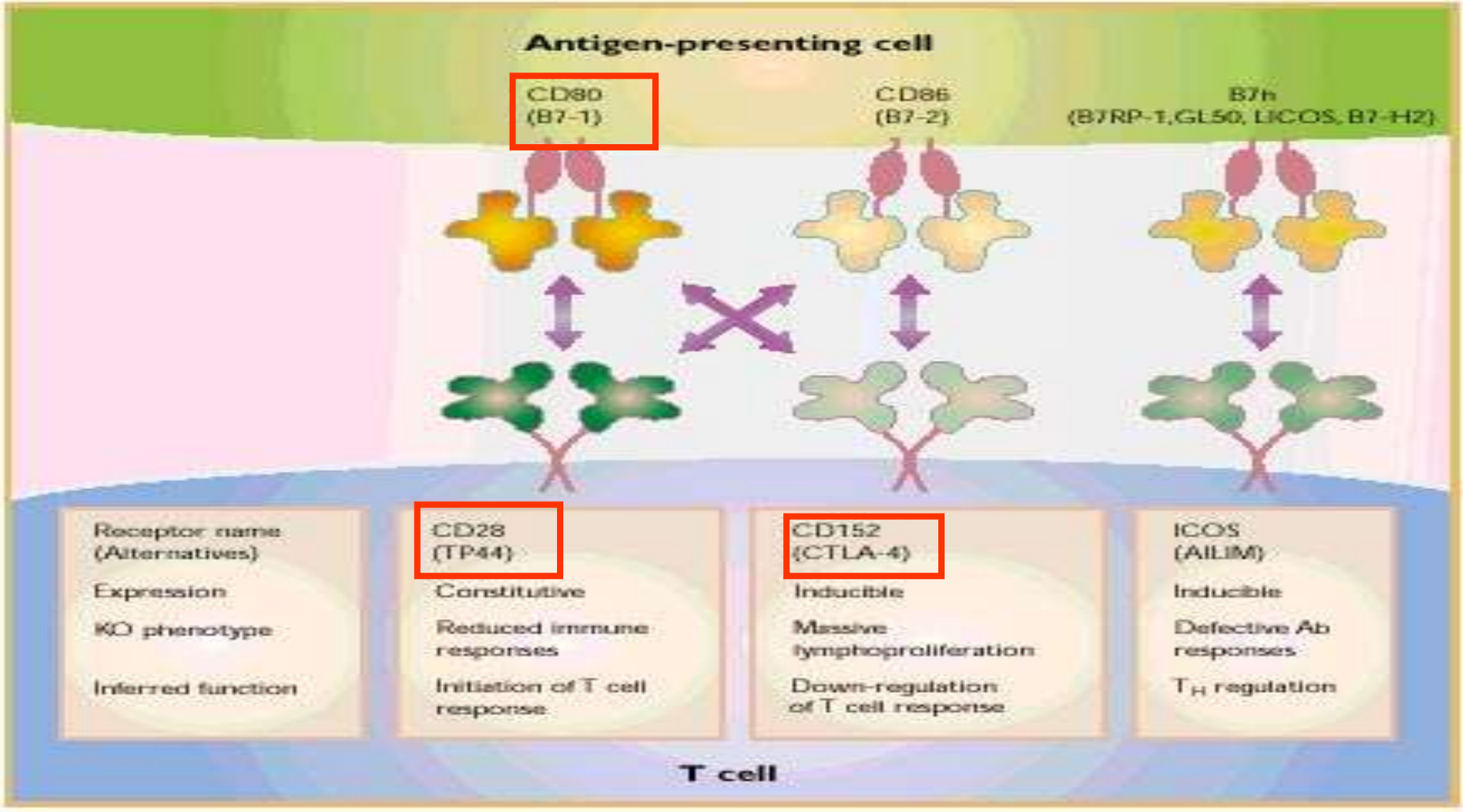
Joanna Marszal Moin A. Saleem



Induction of B7-1 in podocytes is associated with nephrotic syndrome

Jochen Reiser,[1] Gero von Gersdorff,[1] Martin Loos,[1] Jun Oh,[1] Katsuhiko Asanuma,[1] Laura Giardino,[1] Maria Pia Rastaldi,[2] Novella Calvaresi,[2] Haruko Watanabe,[3] Karin Schwarz,[1] Christian Faul,[1,4] Matthias Kretzler,[5] Anne Davidson,[1,6] Hikaru Sugimoto,[7] Raghu Kalluri,[7] Arlene H. Sharpe,[8] Jordan A. Kreidberg,[9] and Peter Mundel[1,4]

J. Clin. Invest. **113**:1390–1397 (2004)

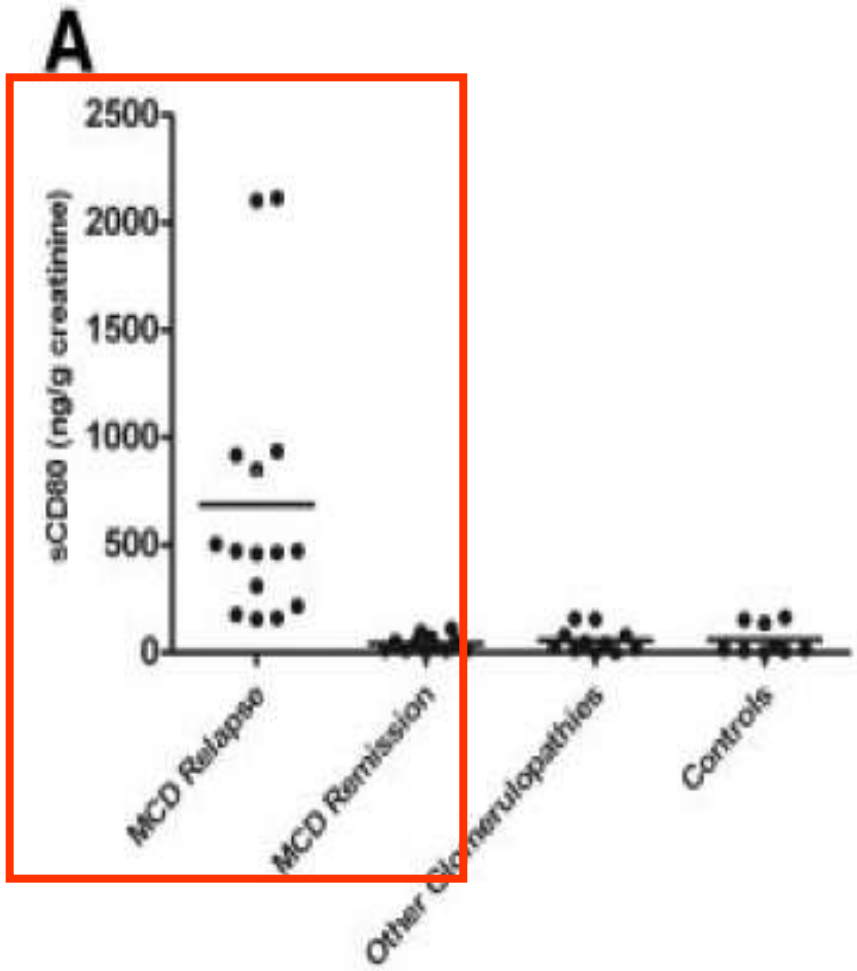


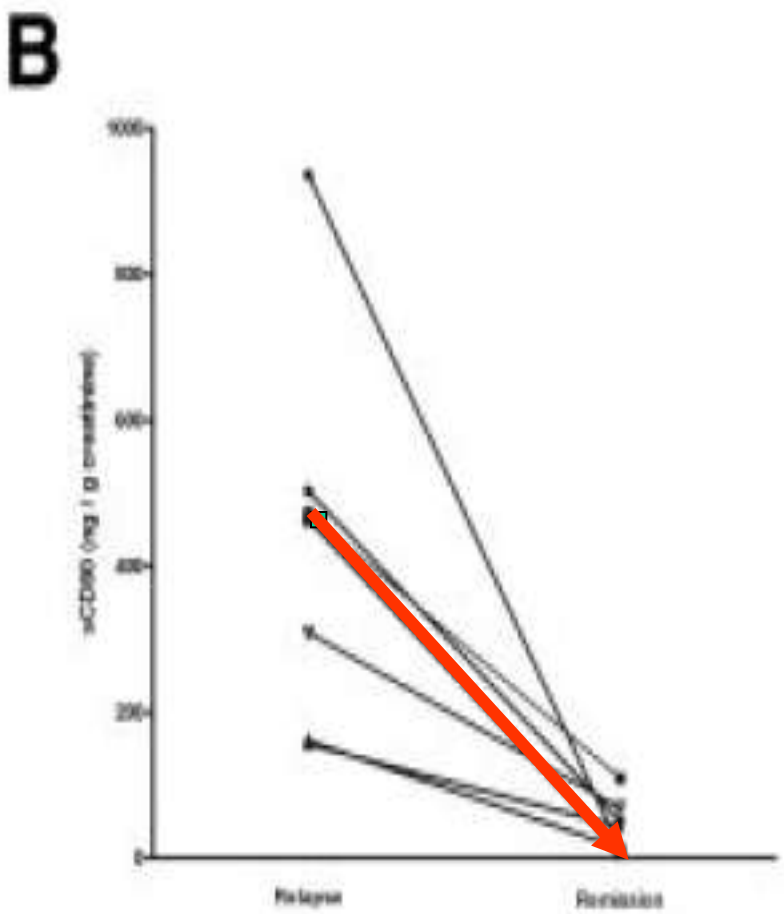
Urinary CD80 Excretion Increases in Idiopathic Minimal-Change Disease

J Am Soc Nephrol ●●: –, 2009.

Eduardo H. Garin,* Leila N. Diaz,* Wei Mu,† Clive Wasserfall,‡ Carlos Araya,* Mark Segal,† and Richard J. Johnson†

Urinary sCD80 increased in pts with MCD relapse, normalized in remission



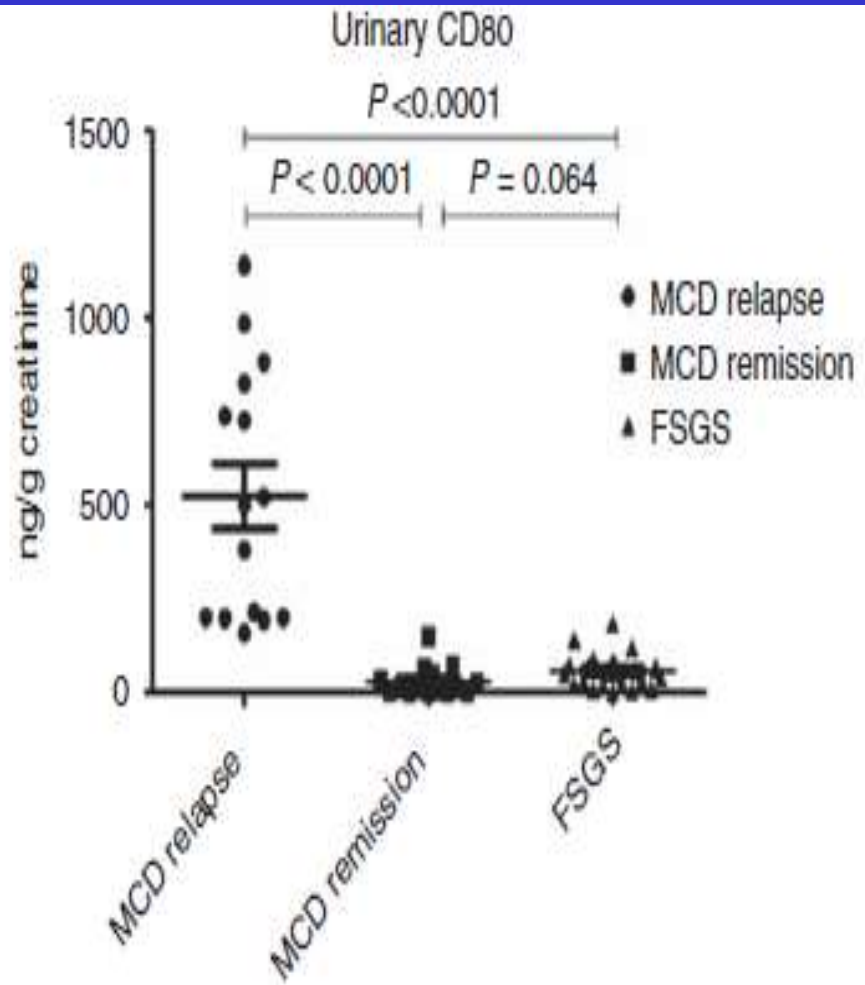


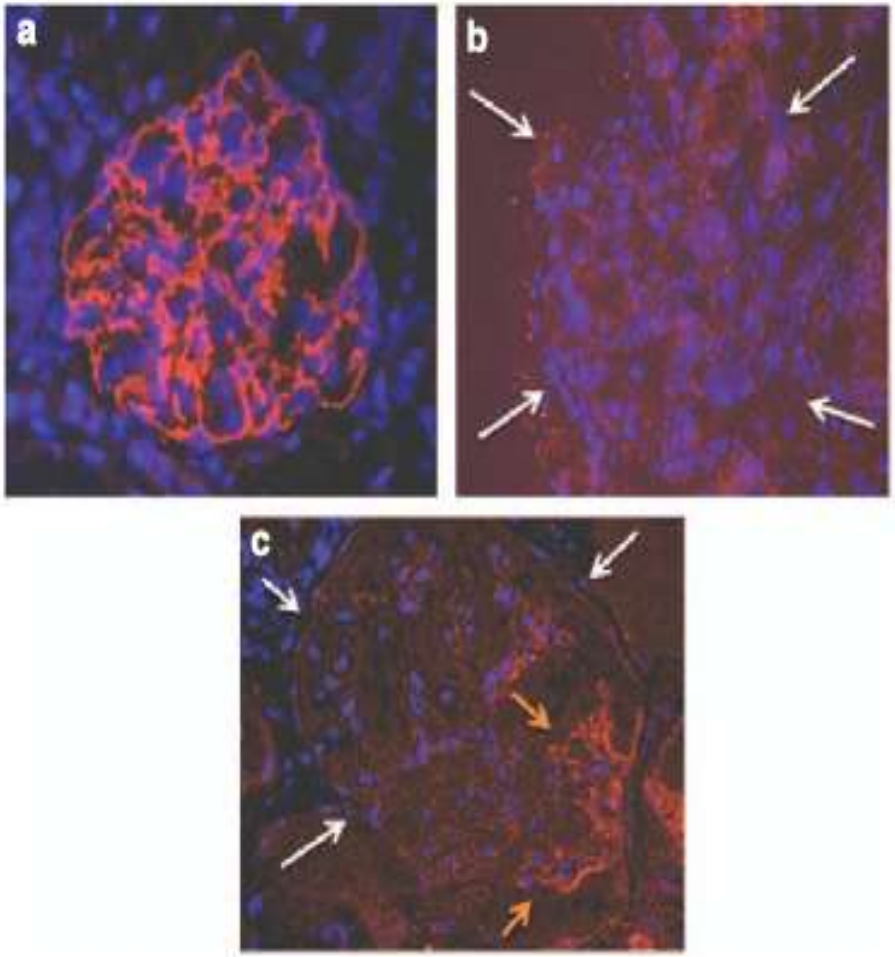
Urinary CD80 is elevated in minimal change disease but not in focal segmental glomerulosclerosis

Eduardo H. Garin[1], Wei Mu[2], John M. Arthur[3], Christopher J. Rivard[4], Carlos E. Araya[1], Michiko Shimada[2,4] and Richard J. Johnson[2,4]

Kidney International (2010) **78,** 296–302

Urinary MCD is increased in relapse of MCD, but not in FSGS

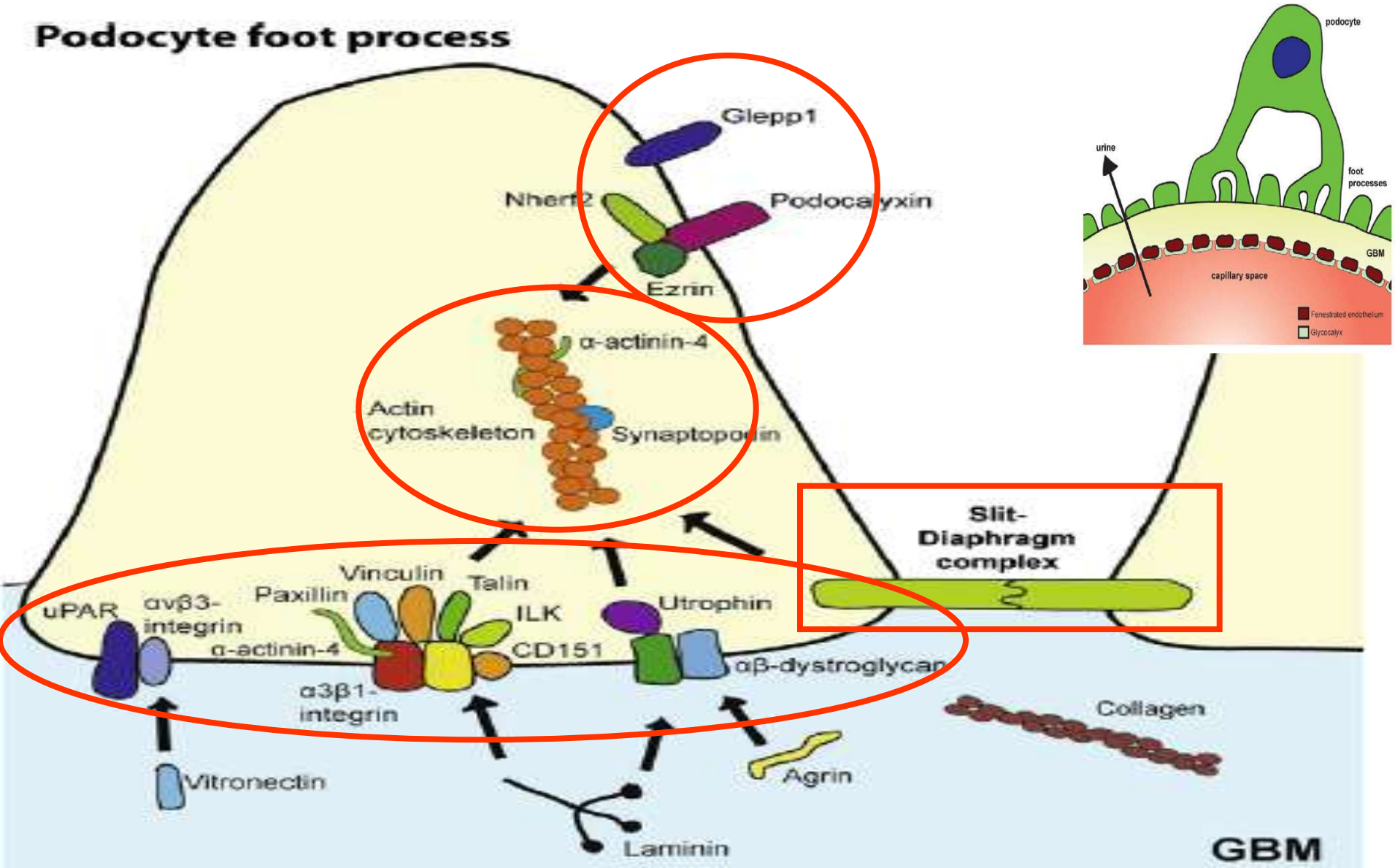




Molecular make-up of the glomerular filtration barrier

Jaakko Patrakka [a,b,*], Karl Tryggvason [a]

Biochemical and Biophysical Research Communications 396 (2010) 164–169

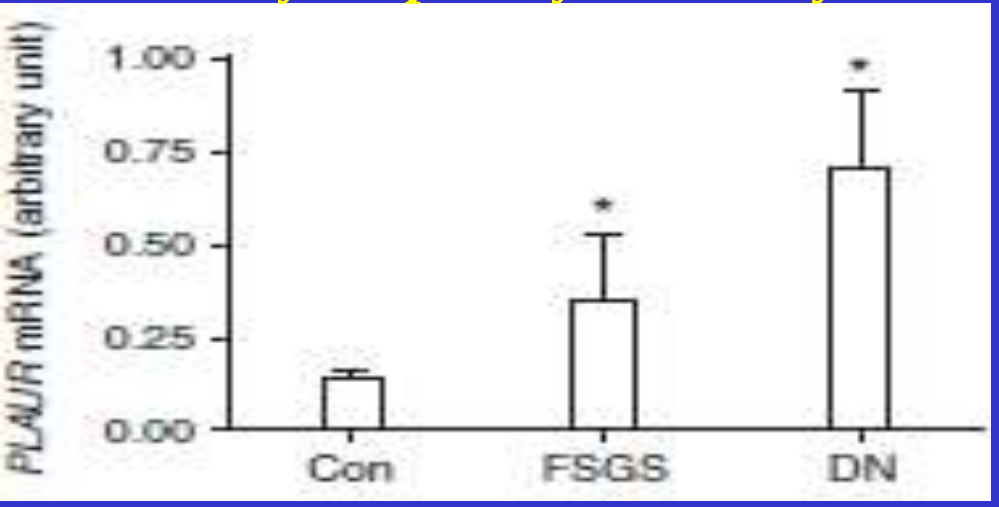


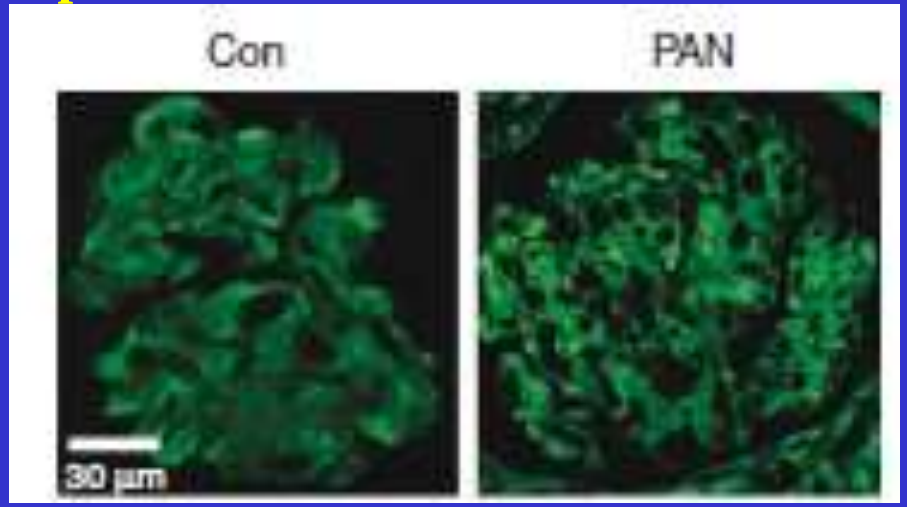
Modification of kidney barrier function by the urokinase receptor

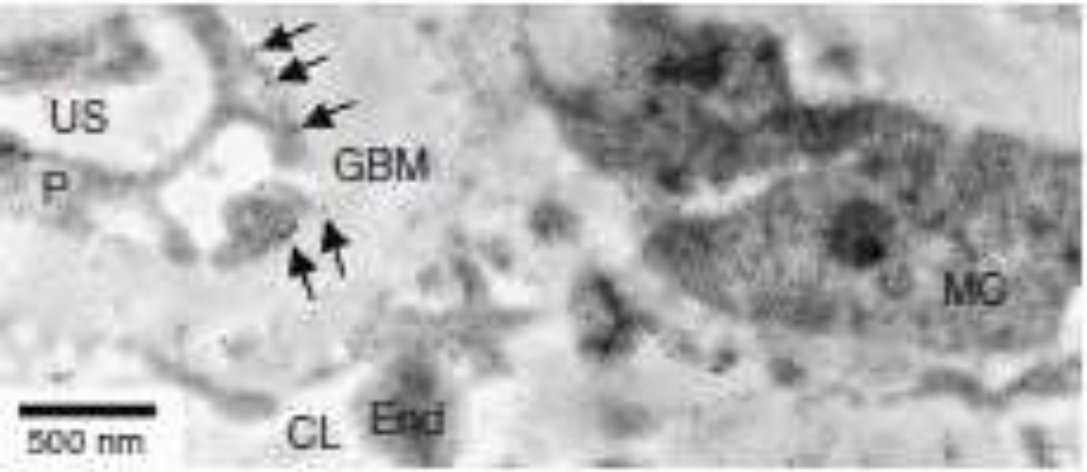
NATURE MEDICINE VOLUME 14 | NUMBER 1 | JANUARY 2008

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]

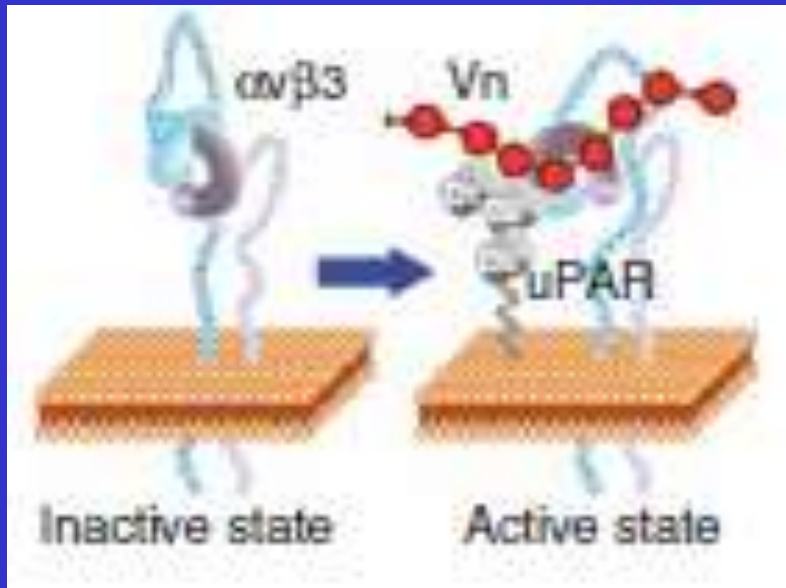
Increased expression of uPAR in proteinuric kidney disease is necessary for podocyte mobility and foot process effacement







Diabetic rat

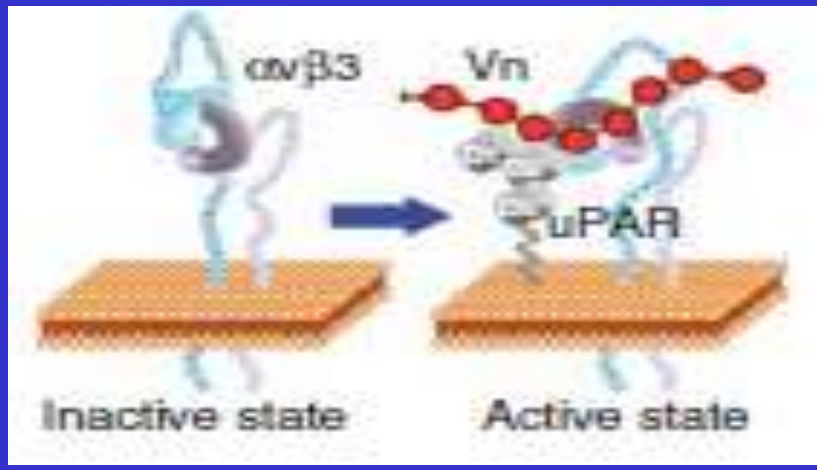


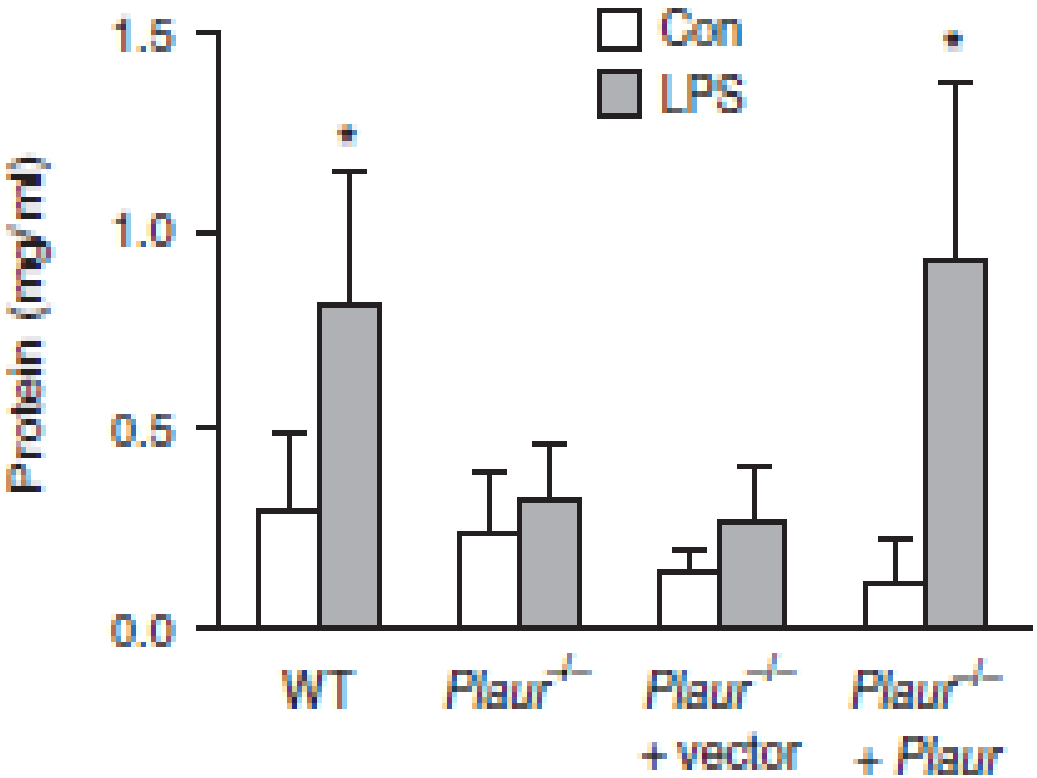
Modification of kidney barrier function by the urokinase receptor

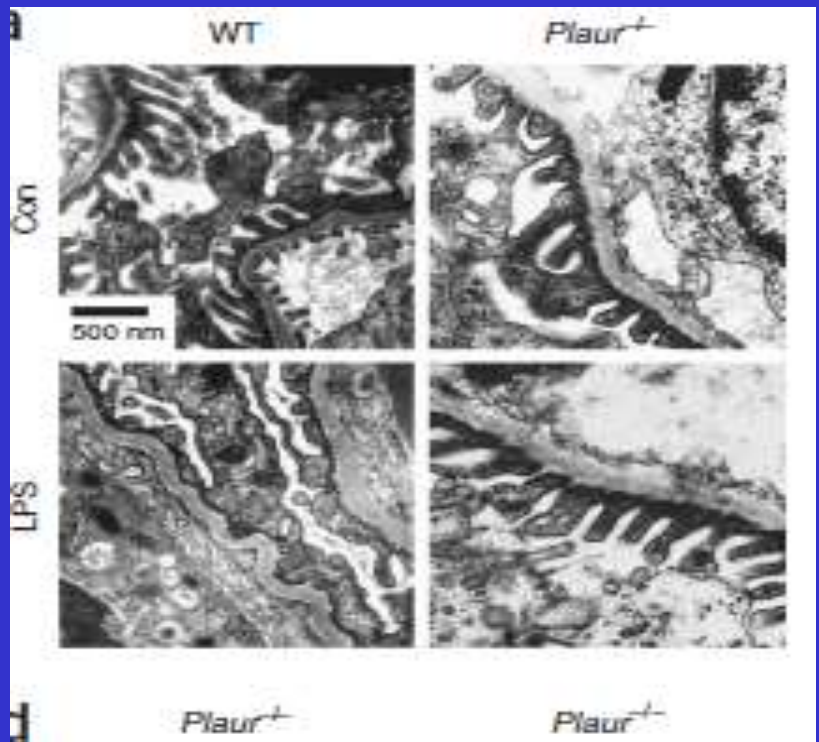
NATURE MEDICINE VOLUME 14 | NUMBER 1 | JANUARY 2008

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]

uPAR knockout prevents LPS-induced proteinuria and foot process effacement





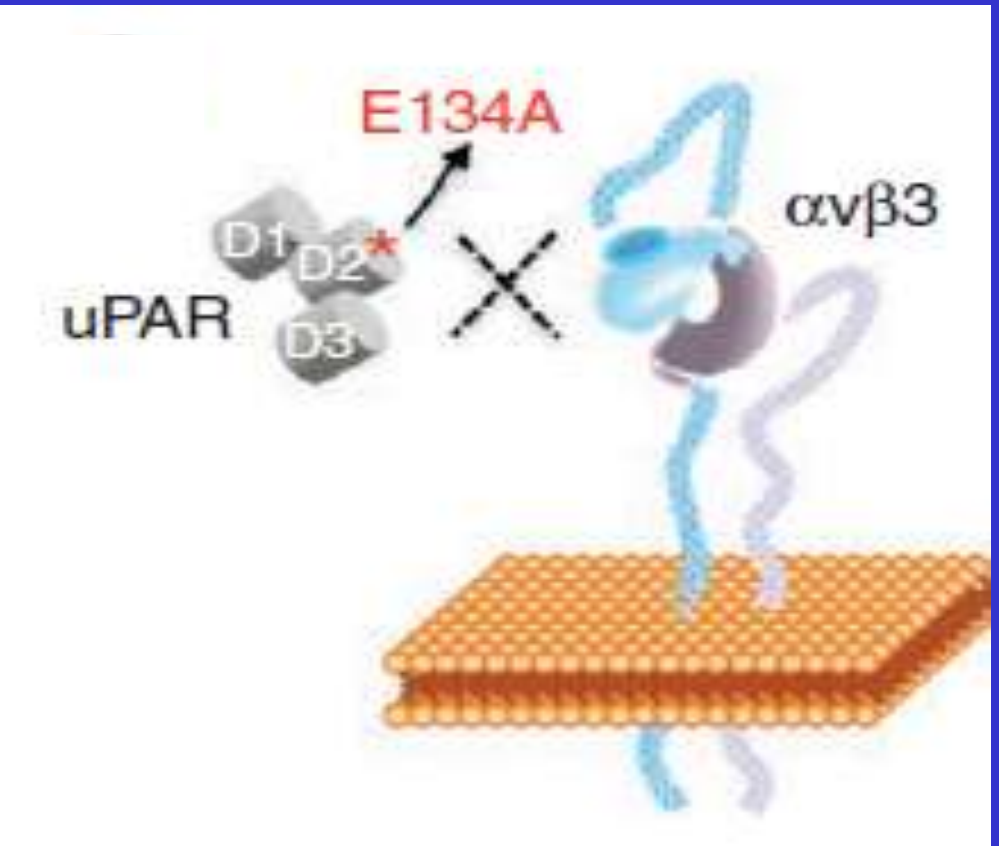


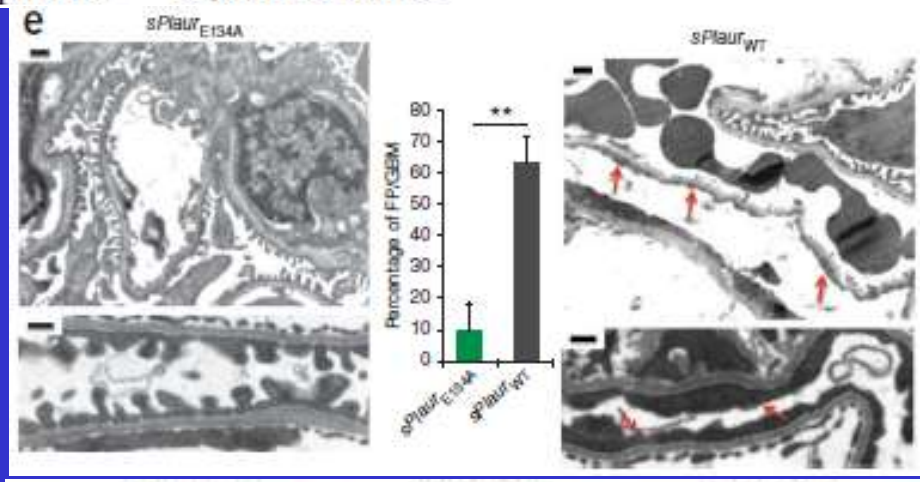
Circulating urokinase receptor as a cause of focal segmental glomerulosclerosis

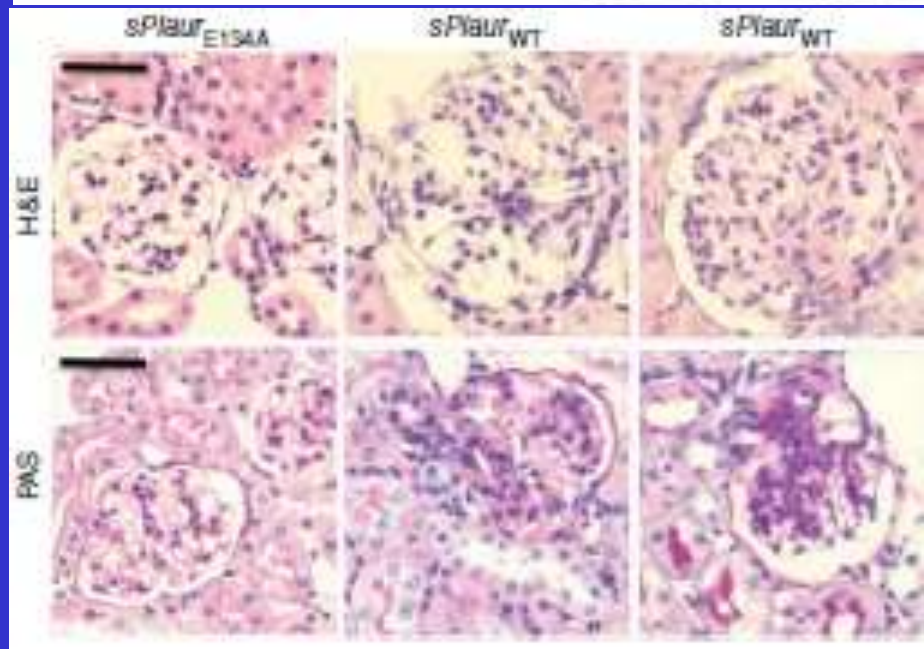
NATURE MEDICINE July 2011

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], Pirouz Daftarian[10,11], Eduardo Salido[12], Armando Torres[12], Moro Salifu[13], Minnie M Sarwal[9], Franz Schaefer[14], Christian Morath[15], Vedat Schwenger[15], Martin Zeier[15], Vineet Gupta[1], David Roth[1], Maria Pia Rastaldi[16], George Burke[4], Phillip Ruiz[4,17] & Jochen Reiser[1]

Circulating suPAR activates podocyte β3 integrin resulting in foot process effacement and FSGS







Circulating urokinase receptor as a cause of focal segmental glomerulosclerosis

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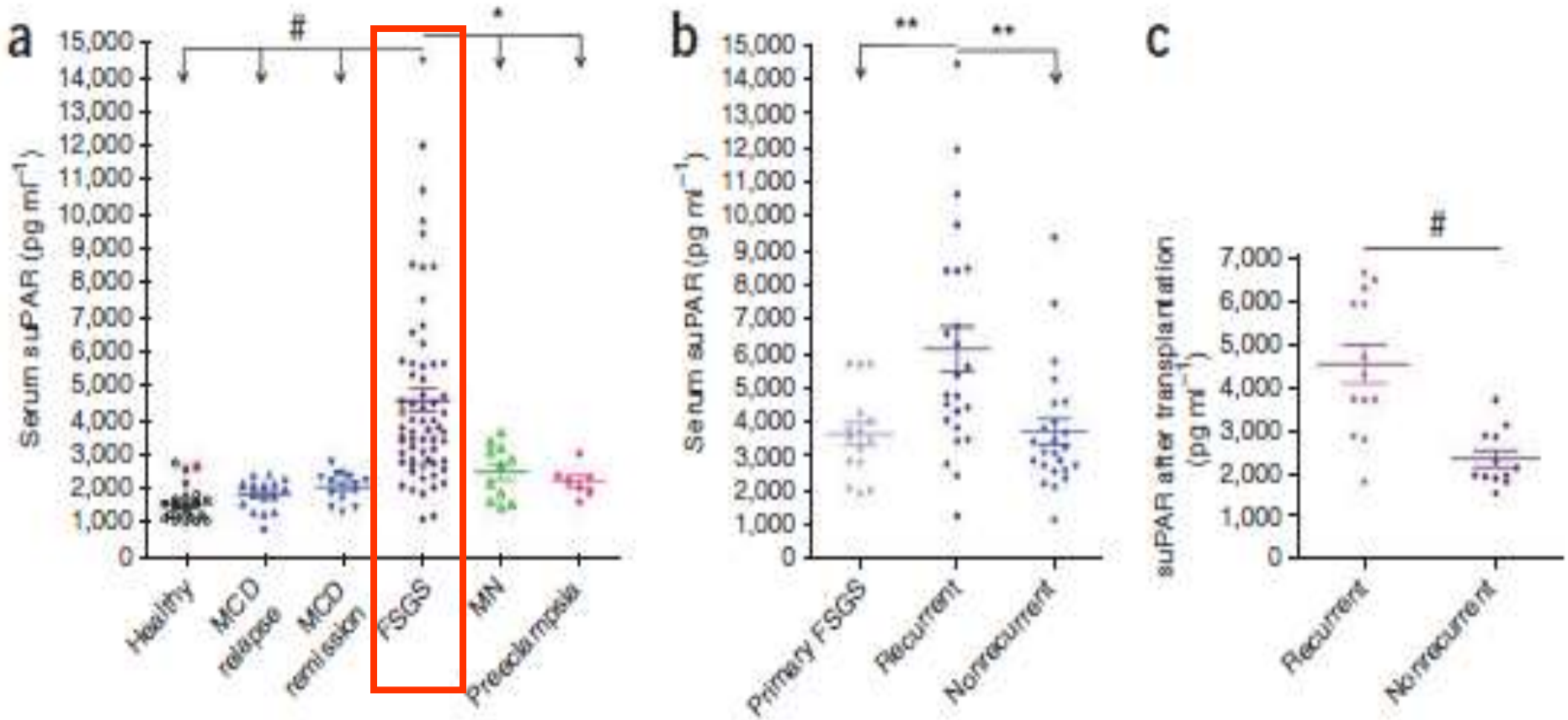
Circulating suPAR is specifically increased in pts with primary FSGS, but not in MCD, or IMN



Circulating urokinase receptor as a cause of focal segmental glomerulosclerosis

NATURE MEDICINE July 2011

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], Pirouz Daftarian[10,11], Eduardo Salido[12], Armando Torres[12], Moro Salifu[13], Minnie M Sarwal[9], Franz Schaefer[14], Christian Morath[15], Vedat Schwenger[15], Martin Zeier[15], Vineet Gupta[1], David Roth[1], Maria Pia Rastaldi[16], George Burke[4], Phillip Ruiz[4,17] & Jochen Reiser[1]

Proteinuria and FSGS could be potentially abrogated by:

1. lowering of serum suPAR levels by plasma exchange
2. antibodies against suPAR
3. small molecules interfering with suPAR/β3 integrin interaction

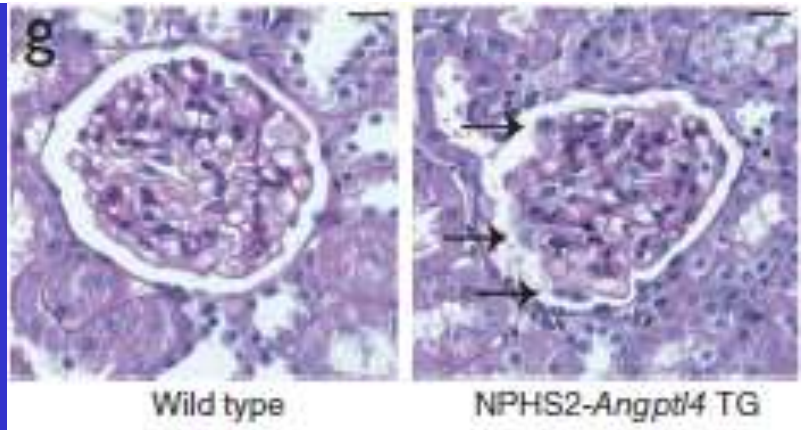
Podocyte-secreted angiopoietin-like-4 mediates proteinuria in glucocorticoid-sensitive nephrotic syndrome

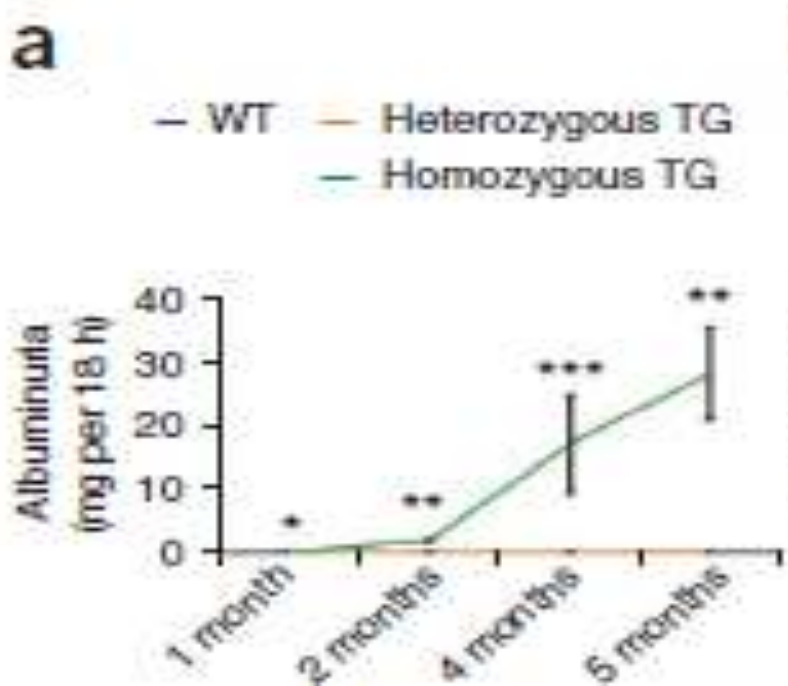
nature medicine

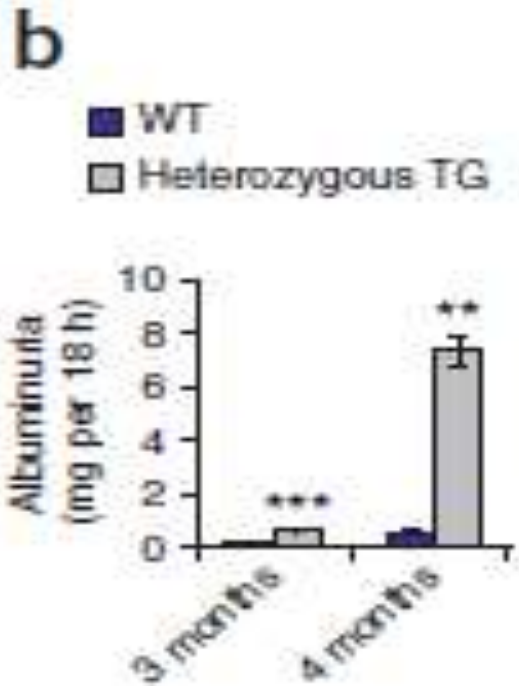
Lionel C Clement[1], Carmen Avila-Casado[2,5], Camille Macé[1,5], Elizabeth Soria[2], Winston W Bakker[3], Sander Kersten[4] & Sumant S Chugh[1]

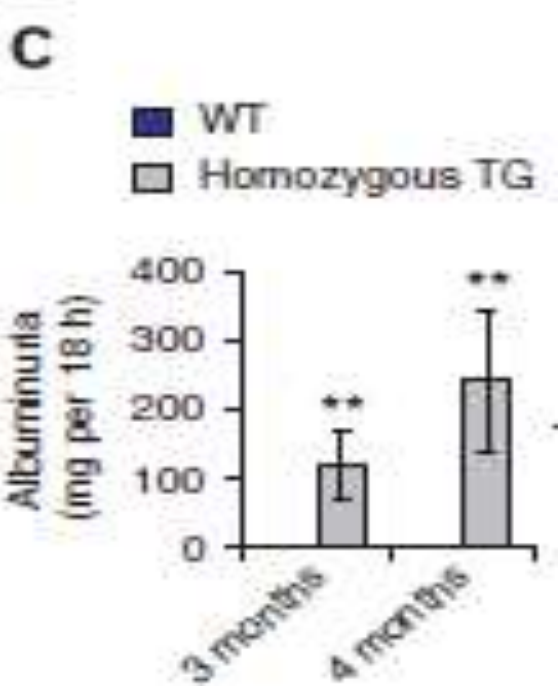
December 2010

Podocyte-derived angiopoietin-like-4 mediates proteinuria in nephrotic syndrome and is glucocorticoid-sensitive









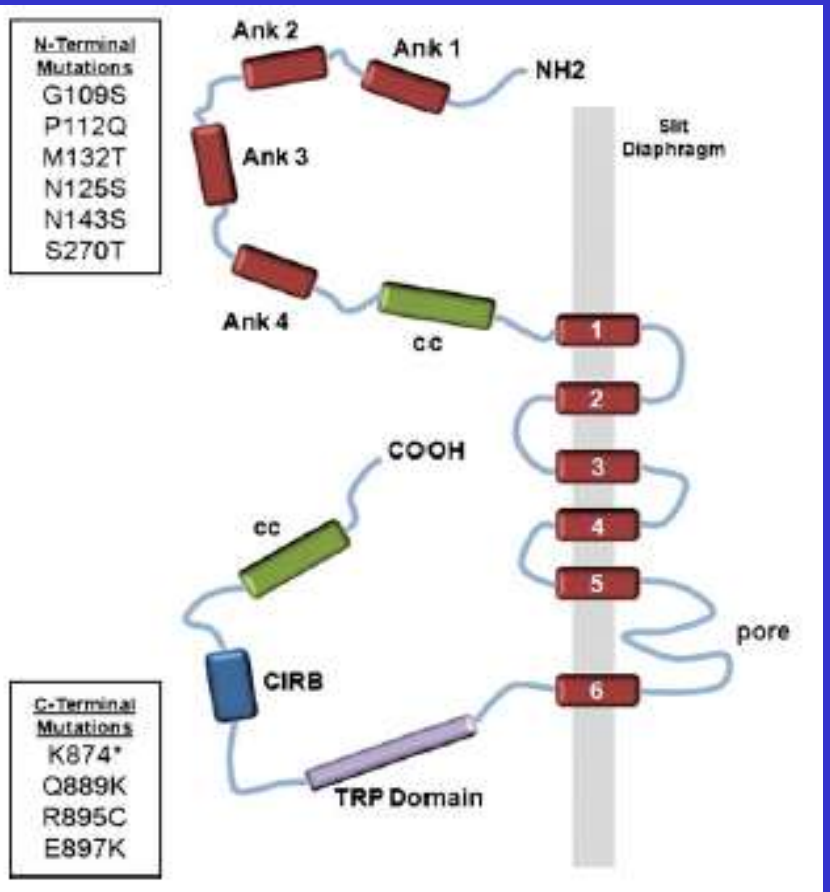
TRPC channel modulation in podocytes—inching toward novel treatments for glomerular disease

Pediatr Nephrol (2011) 26:1057–1064

Shafic El Hindi · Jochen Reiser

TRPC6 is activated not only in rare congenital disease, but also in acquired forms of nephrotic syndrome

Specific inhibitors of TRPC6 or non-specific inhibitors of TRPC with targeted podocyte delivery are actively searched



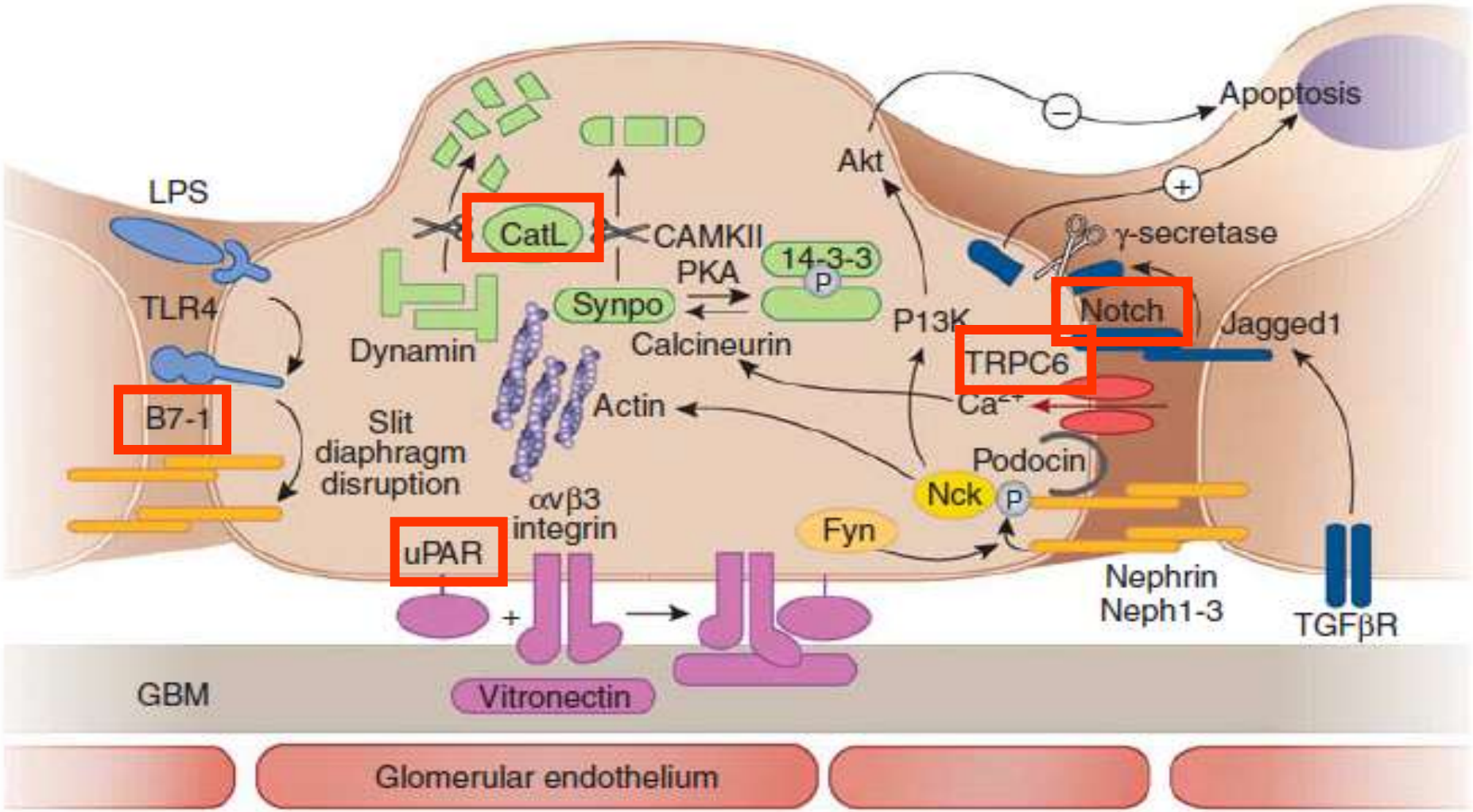
Normal Podocyte	Mutated TRPC6	Increased TRPC6
Normal Barrier Function	Late Onset FSGS	Acute Onset Glomerular Disease (i.e. FSGS, MN)
Physiologic Stress Adaptation	Decreased Stress Adaptation	Disturbed Stress Adaptation
Normal Podocyte Life Span	Decreased Podocyte Life Span	?
No Therapy needed	Standard Therapy: •HTN control •Dyslipidemia control •ACE-I •ARB	Standard Therapy: •HTN control •Dyslipidemia control •ACE-I •ARB Experimental Therapy: •Podocyte specific siRNA delivery •Gene delivery of dominant-negative TRPC6 pore mutant •Specific molecular inhibitors of TRPC6 •Non-specific but target-specific inhibitors of TRPC channels

Toward the development of podocyte-specific drugs

Jochen Reiser[1], Vineet Gupta[1] and Andreas D. Kistler[1]

Kidney International advance online publication, 3 February 2010; doi:10.1038/ki.2009.559

Potential targets of therapeutic interventions in the podocyte



Selected topics

1. classification of podocyte injury – impact on outcome

2. genetic basis of podocyte injury – mutations and polymorphisms

3. molecular mechanisms of podocyte injury in MCD and FSGS

4. do we already have treatment with direct effect on podocyte?

5. news in the pathogenesis of IMN

Direct effect of treatment on podocytes

Inhibition of RAS

actin reorganization,

↑ expression of nephrin and CD2AP

↑ podocyte VEGF production

↓ AT-2 induced FP effacement

Simvastatin maintains steady patterns of GFR and improves AER and expression of slit diaphragm proteins in type II diabetes

G Tonolo[1], M Velussi[2], E Brocco[3], C Abaterusso[4], A Carraro[5], G Morgia[6], A Satta[7], R Faedda[7], A Abhyankar[8], H Luthman[8] and R Nosadini[7,9]

Kidney International (2006) **70,** 177–186.

Table 3 | Mean ± s.e. and geometric mean with range serum and plasma levels of CH, TG, LDL cholesterol, HDL cholesterol, and highly sensitive C-protein-reactive protein (hsCRP) at baseline (B) and after 4 years of simvastatin or cholestyramine treatment

	CH (mg/dl)	TG (mg/dl)	LDL (mg/dl)	HDL (mg/dl)	HsCRP (mg/l)
Simvastatin					
B	231 ± 12	191 ± 45	150 ± 13	43 ± 5	2.25 (0.7-2.99)
4 years	170 ± 13*	148 ± 39*	99 ± 15*	42 ± 6	2.19 (0.8-2.81)
Cholestyramine					
B	227 ± 16	188 ± 50	148 ± 16	44 ± 7	2.11 (0.7-2.70)
4 years	166 ± 18*	146 ± 48*	97 ± 18*	45 ± 8	2.13 (0.6-2.90)

Table 4 | Mean ± s.e. urinary 8-OH-dG levels (μg/g creatinine) in type 2 hypertensive microalbuminuric diabetic patients (82) at baseline, and in 42 after 4-year simvastatin and in 40 after 4-year cholestyramine treatment

	Baseline	4th year
Simvastatin	4.45 ± 0.15	3.20 ± 0.20**
Cholestyramine	4.49 ± 0.11	3.91 ± 0.14^{NS}

8-OH-dG: 8-hydroxydeoxyguanosine.
Group 1: Simvastatin treated patients.
Group 2: Cholestyramine treated patients.
**$P < 0.01$ baseline vs 4th year.
NS=not significant baseline vs 4th year.

Table 5 | Mean ± s.e. and median with ranges of GFR and AER at baseline and after 4 years treatment with simvastatin and cholestyramine

	GFR (ml/min/1.73m^2)	AER (μg/mg)	Normo	Prot.
Simvastatin				
B	91 ± 8	77 (31–259)	—	—
4 years	90 ± 7	40* (10–319)	29%	4%
Cholestyramine				
B	90 ± 7	88 (34–261)	—	—
4 years	79 ± 8***	81 (17–399)	8%**	15%**

Simvastatin maintains steady patterns of GFR and improves AER and expression of slit diaphragm proteins in type II diabetes

G Tonolo[1], M Velussi[2], E Brocco[3], C Abaterusso[4], A Carraro[5], G Morgia[6], A Satta[7], R Faedda[7], A Abhyankar[8], H Luthman[8] and R Nosadini[7,9]

Kidney International (2006) **70,** 177–186.

Simvastatin

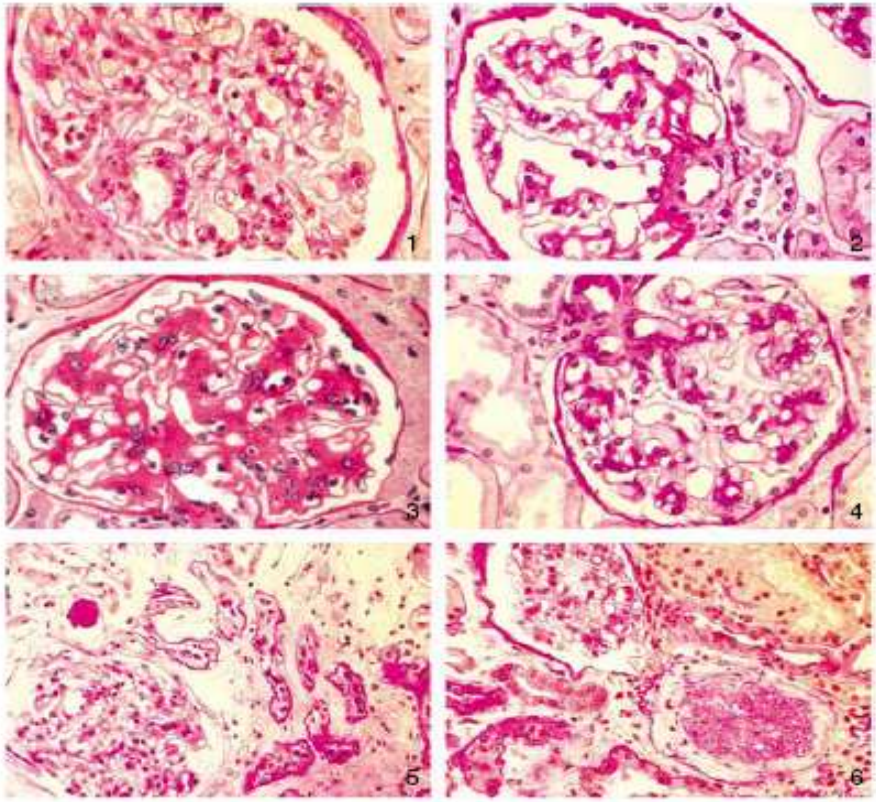


Figure 1 | Patterns of the glomerular and renal lesions in kidney specimens from Categories 1–3 patients at baseline (panels 1, 3, and 5) and after simvastatin treatment (panels 2, 4, and 6).

Cholestyramin

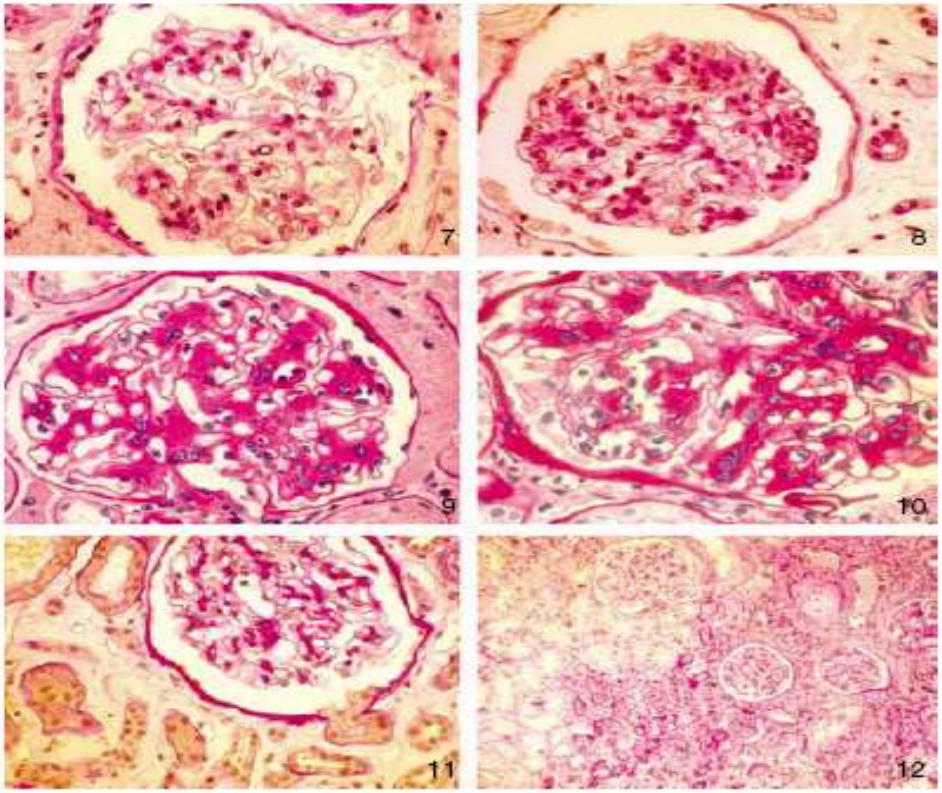


Figure 2 | Patterns of the glomerular and renal lesions in kidney specimens from Categories 1–3 patients at baseline (panels 7, 9, and 11) and after cholestyramine treatment (panels 8, 9, and 12).

PPAR-γ agonist protects podocytes from injury

T Kanjanabuch[1], L-J Ma[1], J Chen[1], A Pozzi[2], Y Guan[2], P Mundel[3] and AB Fogo[1,2]

[1]*Department of Pathology, Vanderbilt University Medical Center, Nashville, Tennessee, USA;* [2]*Department of Medicine, Vanderbilt University Medical Center, Nashville, Tennessee, USA and* [3]*Division of Nephrology, Mt. Sinai School of Medicine, New York, New York, USA*

Kidney International (2007) **71,** 1232–1239;

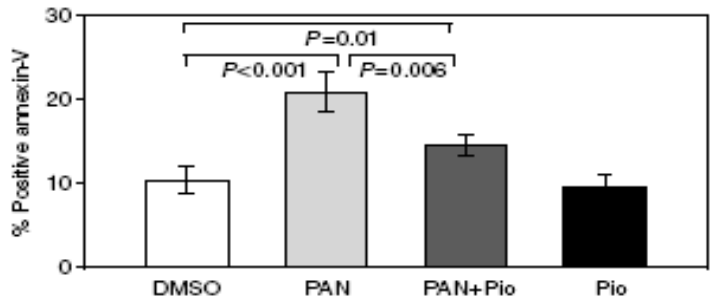


Figure 4 | Apoptosis in PAN-injured podocytes. Fully differentiated

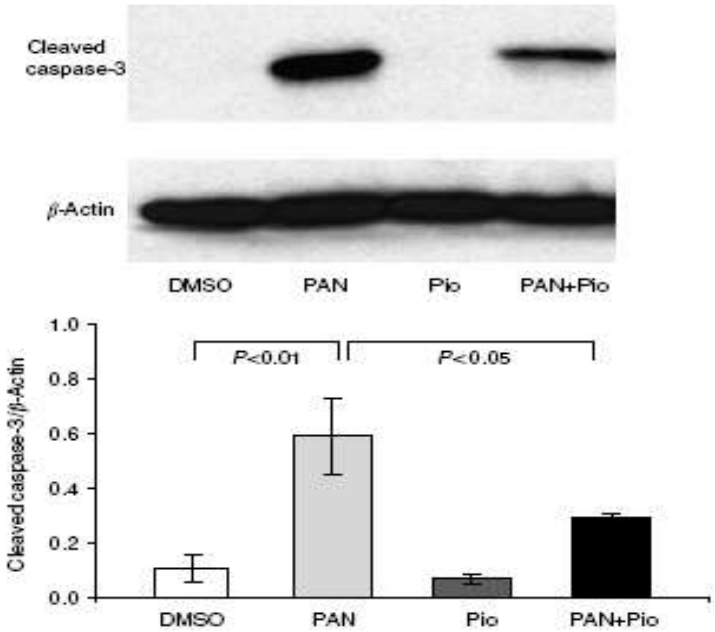


Figure 6 | Activated caspase-3 expression in podocytes. Protein

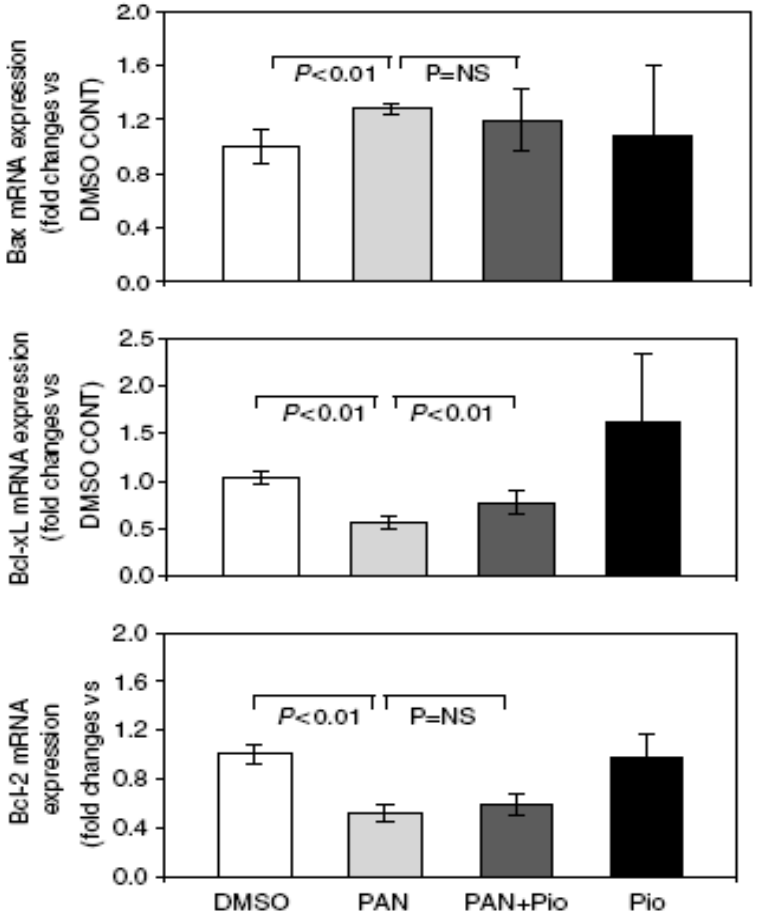


Figure 5 | Apoptotic regulatory molecule mRNA expression in podocytes. Total RNA from podocytes was harvested and Bax, Bcl-xL,

Direct effect of treatment on podocytes

Corticosteroids

↑ expression of CNTF and hsp27,
↓ expression of lysosomal ATP-driven pump,
↓ endoplasmic reticulum stress

↓ podocyte apoptosis

Cyclosporine

normalization of ZO-1 expression

remission in patients with PLCE1 mutation

Dexamethasone Prevents Podocyte Apoptosis Induced by Puromycin Aminonucleoside: Role of p53 and Bcl-2–Related Family Proteins

Takehiko Wada, Jeffrey W. Pippin, Caroline B. Marshall, Sian V. Griffin, and Stuart J. Shankland

J Am Soc Nephrol 16: 2615–2625, 2005

Apoptosis **Loss of viable podocytes**

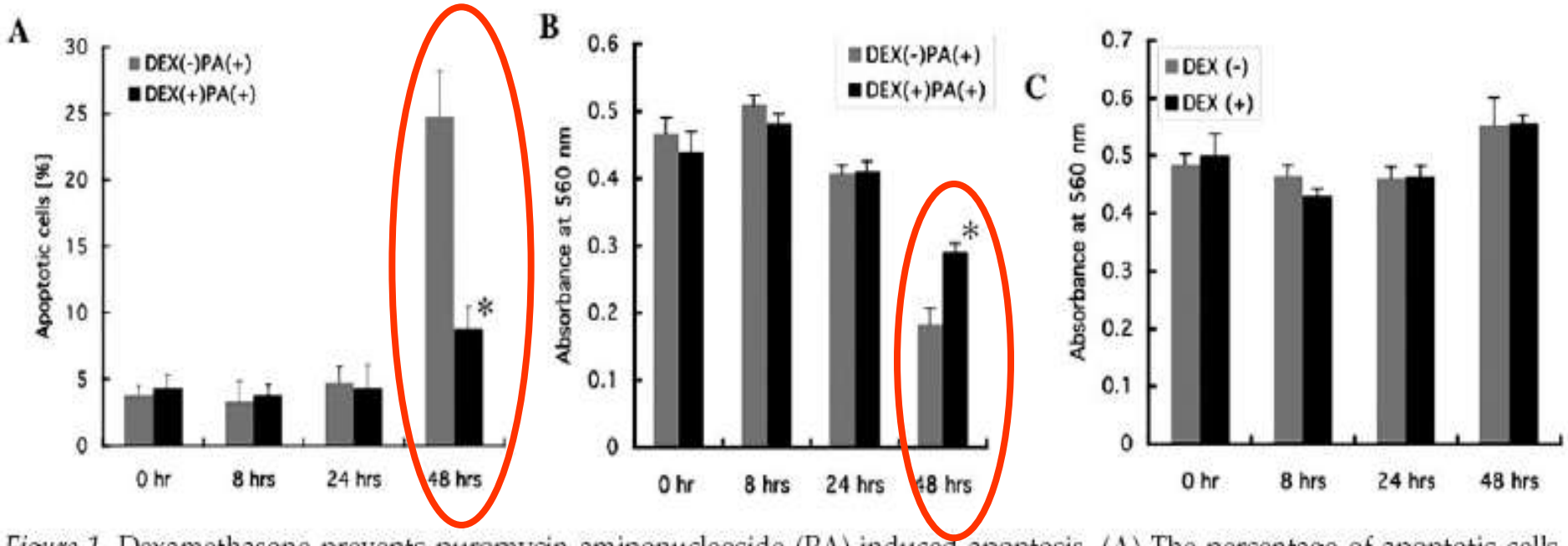


Figure 1. Dexamethasone prevents puromycin aminonucleoside (PA)-induced apoptosis. (A) The percentage of apoptotic cells, measured by Hoechst 33342 staining, increased at 48 h in the cells that were exposed to PA without dexamethasone (DEX; ▨), whereas cells that were treated with DEX were resistant to PA-induced apoptosis (■). *$P < 0.005$ *versus* DEX(−)PA(+). (B) The methylthiazoletetrazolium (MTT) assay showed that the incubation with PA (30 μg/ml) caused the loss of viable podocytes (▨) and that DEX (■) prevented this. *$P < 0.0001$ *versus* DEX(−)PA(+). (C) The MTT assay showed that DEX alone did not affect viable podocyte number.

Direct effects of dexamethasone on human podocytes

C-Y Xing[1,2], MA Saleem[1], RJ Coward[1], L Ni[1], IR Witherden[1] and PW Mathieson[1]

Kidney International (2006) **70,** 1038–1045

Glucocorticoid receptor expression

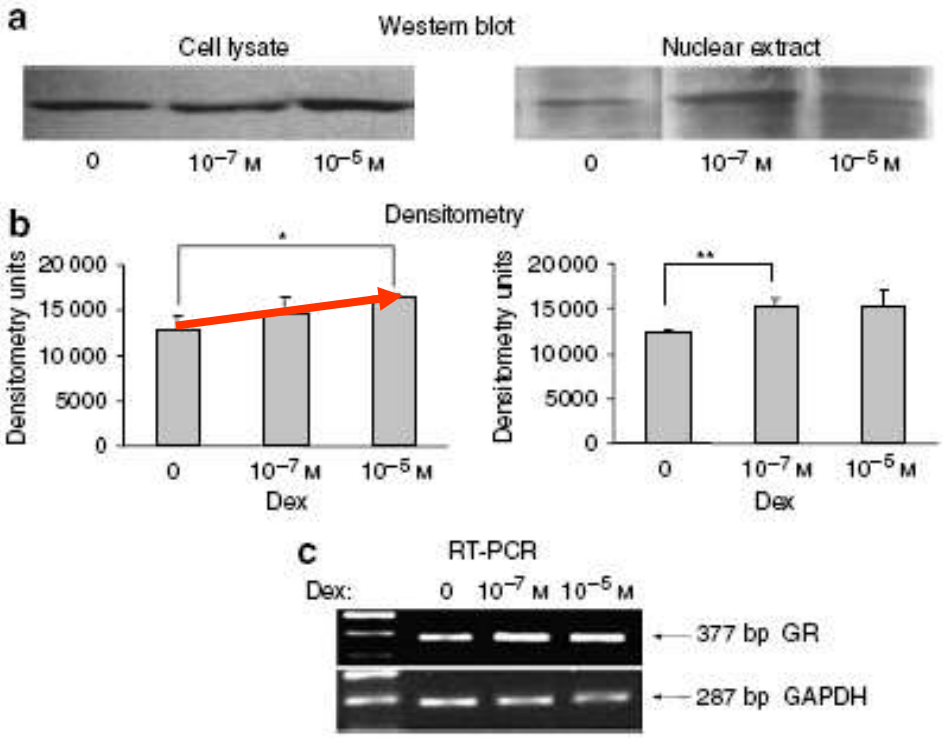


Figure 1 | Effects of dexamethasone on expression of glucocorticoid receptors in human podocytes. (**a**) Representative Western blot on whole-cell lysates and nuclear extracts. (**b**) Densitometry of five replicate Western blots for cell lysates, and three replicate Western blots for nuclear extracts (*$P<0.05$, **$P<0.01$). (**c**) RT-PCR on podocyte RNA using primers for glucocorticoid receptor (GR) and control 'housekeeping' gene (GAPDH) (representative of three replicate experiments).

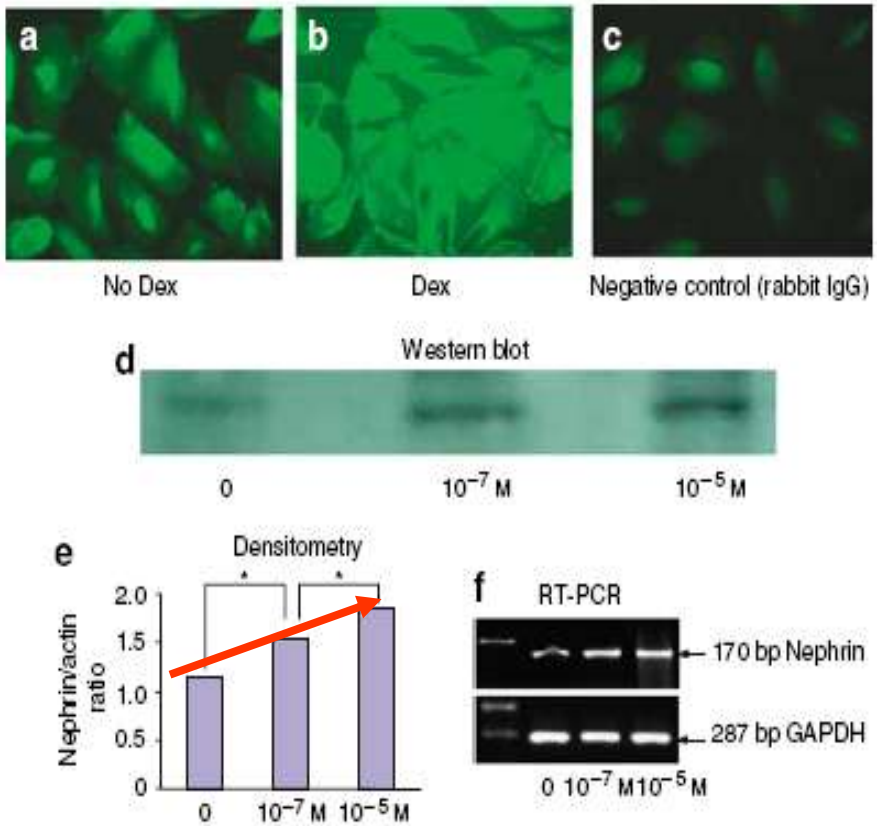


Figure 2 | Effects of dexamethasone on the expression of nephrin in human podocytes. (**a–c**) Effect of incubation with

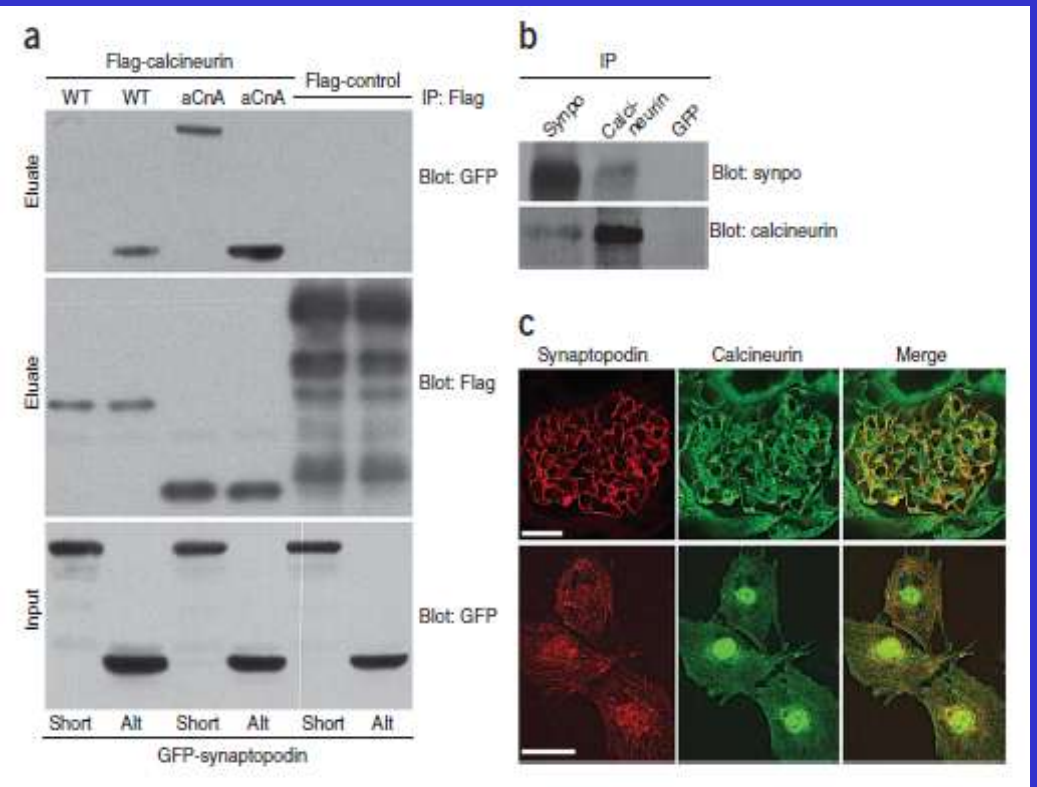
Nephrin expression

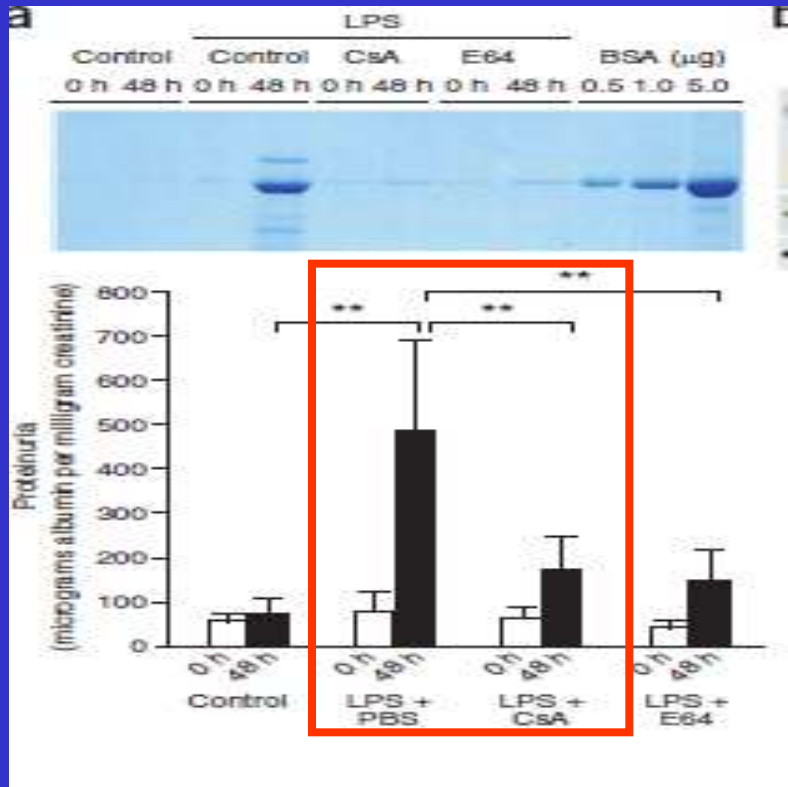
The actin cytoskeleton of kidney podocytes is a direct target of the antiproteinuric effect of cyclosporine A

Christian Faul[1,2], Mary Donnelly[1,2], Sandra Merscher-Gomez[1,2], Yoon Hee Chang[2,5], Stefan Franz[2,5], Jacqueline Delfgaauw[2,5], Jer-Ming Chang[3], Hoon Young Choi[2], Kirk N Campbell[1,2], Kwanghee Kim[2], Jochen Reiser[1,4] & Peter Mundel[1,2]

NATURE MEDICINE VOLUME 14 | NUMBER 9 | SEPTEMBER 2008

The immunosuppressive action of the calcineurin inhibitor cyclosporine A (CsA) stems from the inhibition of nuclear factor of activated T cells (NFAT) signaling in T cells. CsA is also used for the treatment of proteinuric kidney diseases. As it stands, the antiproteinuric effect of CsA is attributed to its immunosuppressive action. Here we show that the beneficial effect of CsA on proteinuria is not dependent on NFAT inhibition in T cells, but rather results from the stabilization of the actin cytoskeleton in kidney podocytes. CsA blocks the calcineurin-mediated dephosphorylation of synaptopodin, a regulator of Rho GTPases in podocytes, thereby preserving the phosphorylation-dependent synaptopodin–14-3-3β interaction. Preservation of this interaction, in turn, protects synaptopodin from cathepsin L–mediated degradation. These results represent a new view of calcineurin signaling and shed further light on the treatment of proteinuric kidney diseases. Novel calcineurin substrates such as synaptopodin may provide promising starting points for antiproteinuric drugs that avoid the serious side effects of long-term CsA treatment.





The NEW ENGLAND JOURNAL of MEDICINE

CLINICAL IMPLICATIONS OF BASIC RESEARCH

Proteinuria and Immunity — An Overstated Relationship?

Peter W. Mathieson, Ph.D.

N ENGL J MED 359;23 WWW.NEJM.ORG DECEMBER 4, 2008

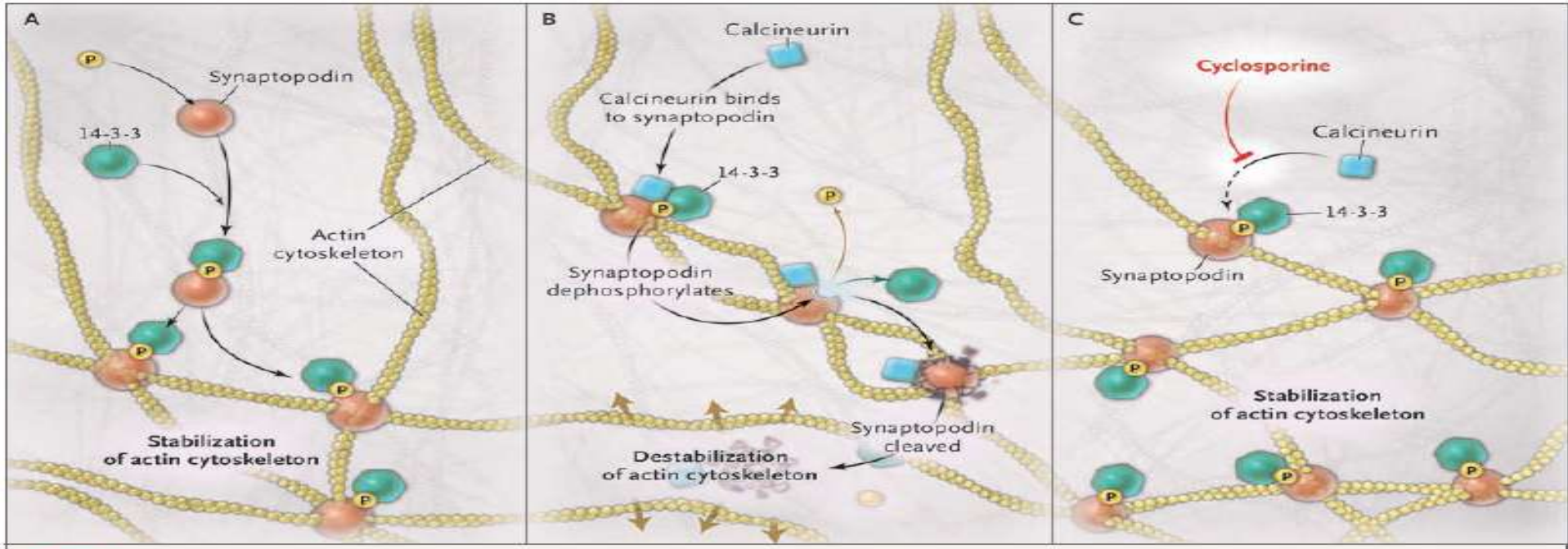


Figure 2. The Effect of Calcineurin on Synaptopodin.

Synaptopodin, when phosphorylated, binds to the 14-3-3 protein and is protected from degradation. Synaptopodin stabilizes the actin cytoskeleton, allowing the podocyte to maintain its shape (Panel A). Calcineurin dephosphorylates synaptopodin, which then separates from 14-3-3 and can be degraded by cathepsin L. Its stabilizing effect on the actin cytoskeleton is lost, and the cell loses its shape (Panel B). Cyclosporin inhibits the action of calcineurin, preventing dephosphorylation of synaptopodin and allowing its actin-stabilizing effect to continue (Panel C). P denotes phosphorylation.

Selected topics

1. classification of podocyte injury – impact on outcome

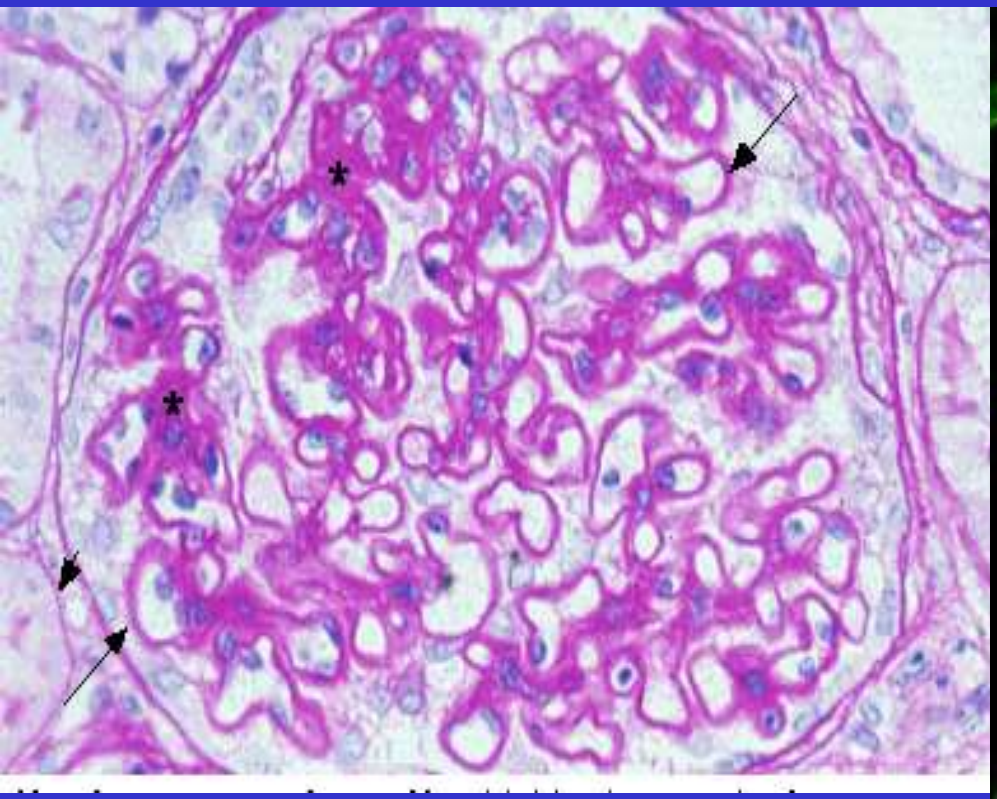
2. genetic basis of podocyte injury – mutations and polymorphisms

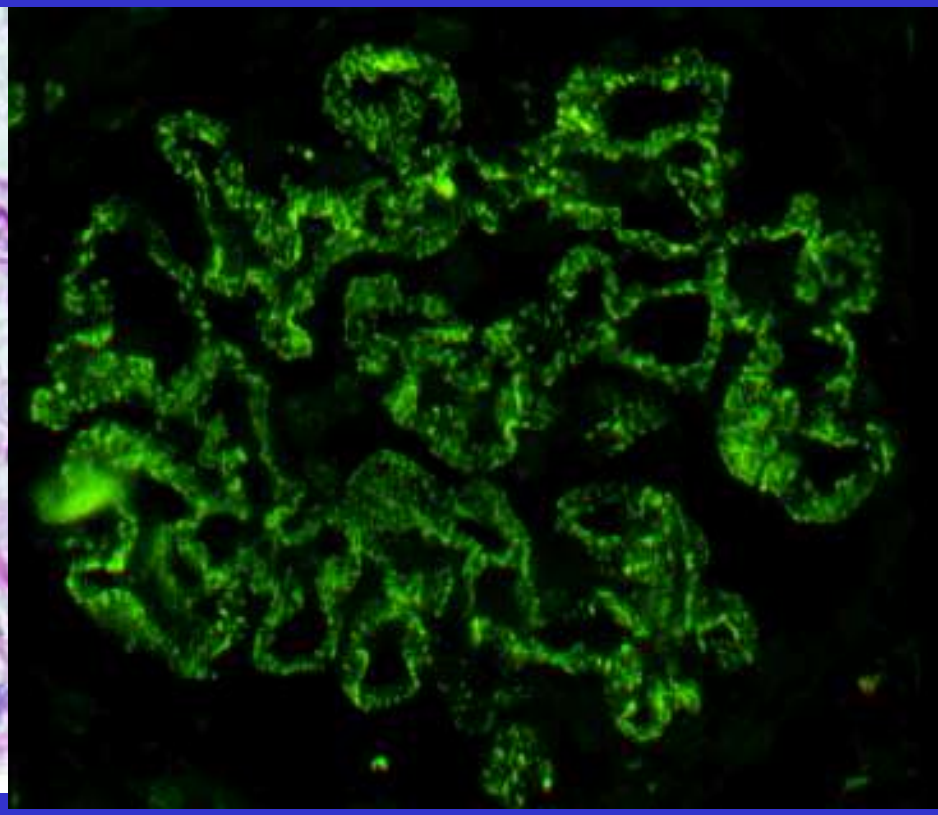
3. molecular mechanisms of podocyte injury in MCD and FSGS

4. do we already have treatment with direct effect on podocyte?

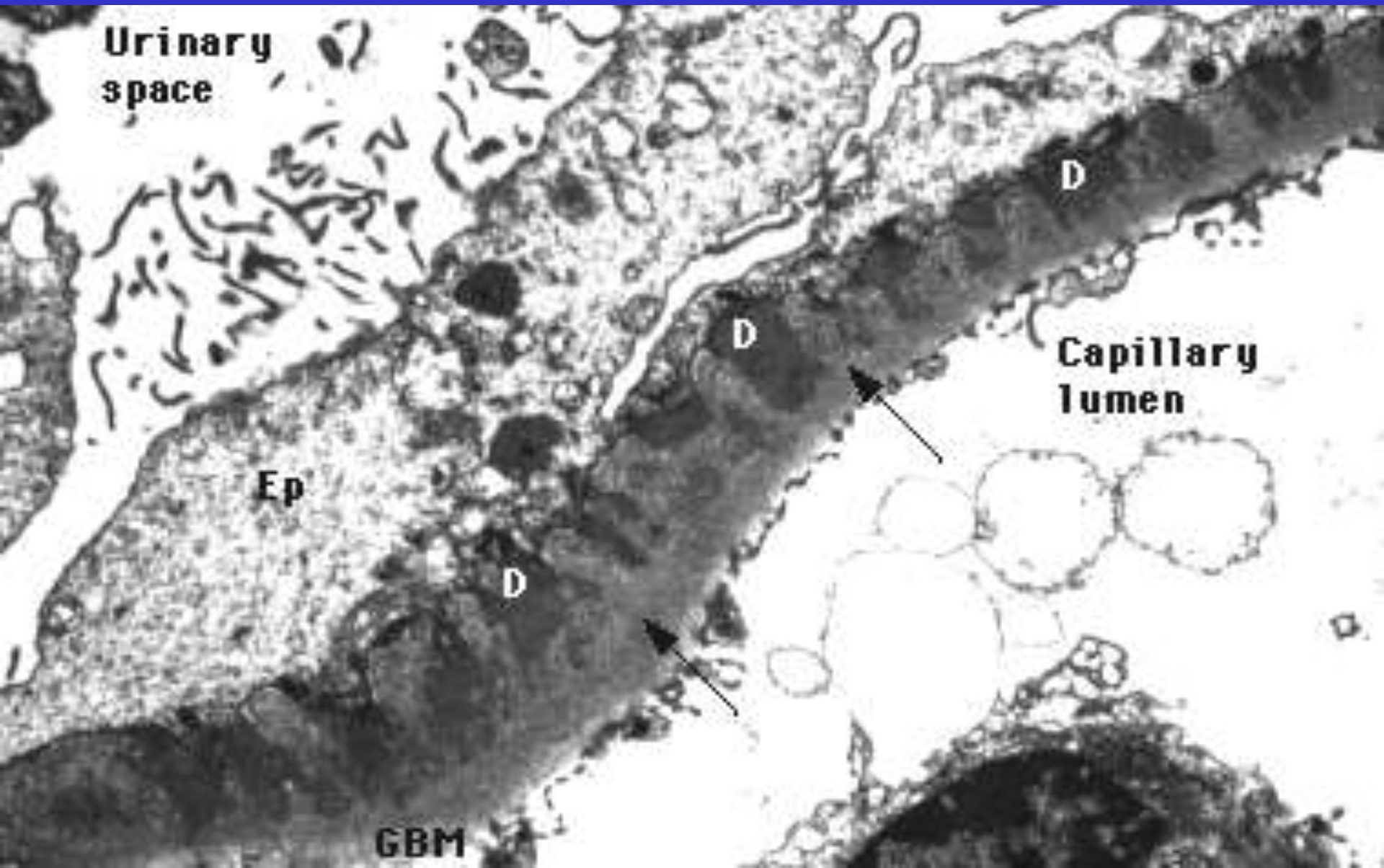
5. news in the pathogenesis of IMN

Membranous nephropathy





Membranous nephropathy

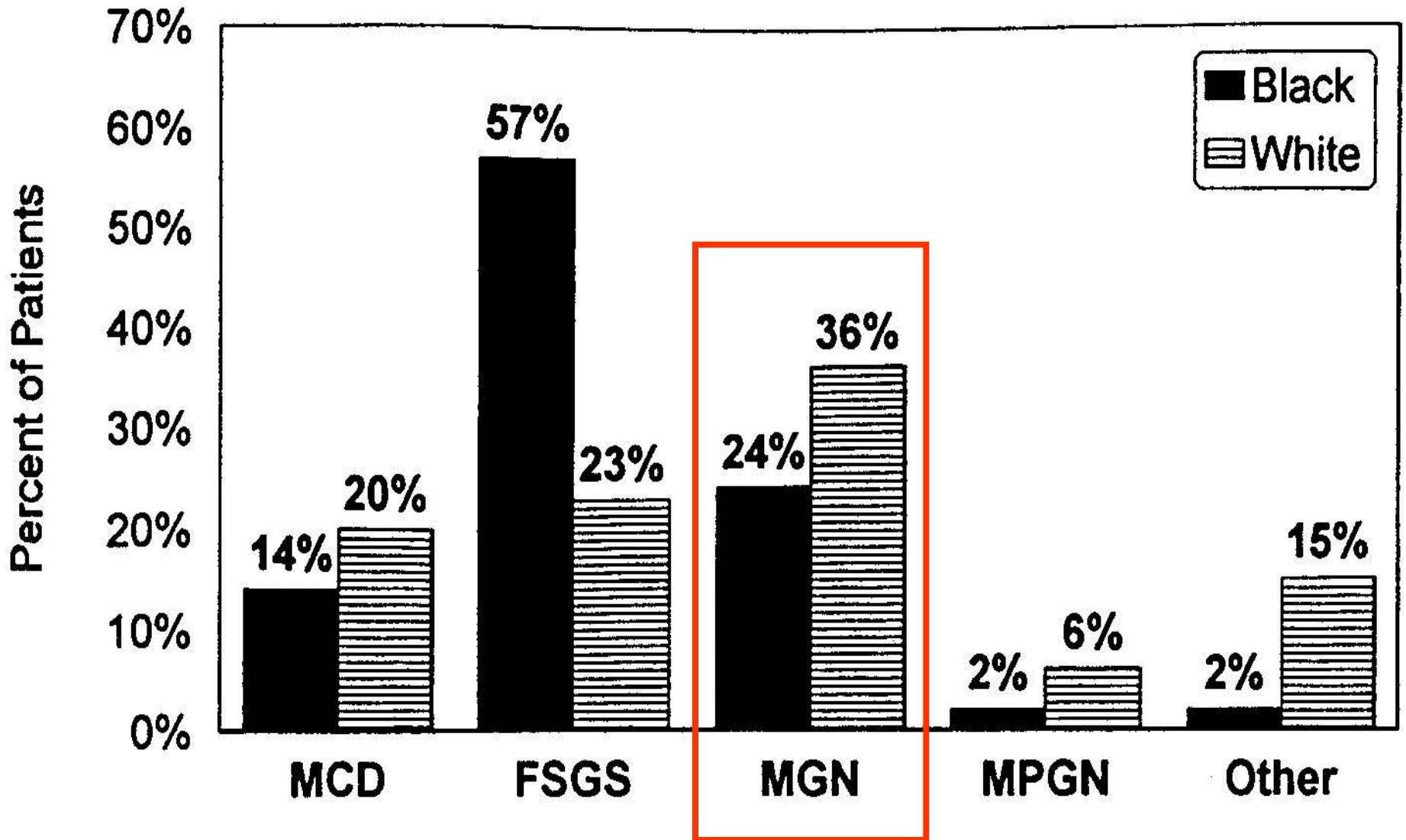


Membranous nephropathy

1. Secondary – planted antigens?
   - infections
     (hepatitis B, syphilis, malaria)
   - drugs
     (organic gold, penicillamine, NSAID)
   - neoplasms
     (carcinomas, e.g. Colon, lung, or stomach, and lymphomas)
   - systemic lupus erythematosus
2. Idiopathic – antibodies directed to podocyte antigens?

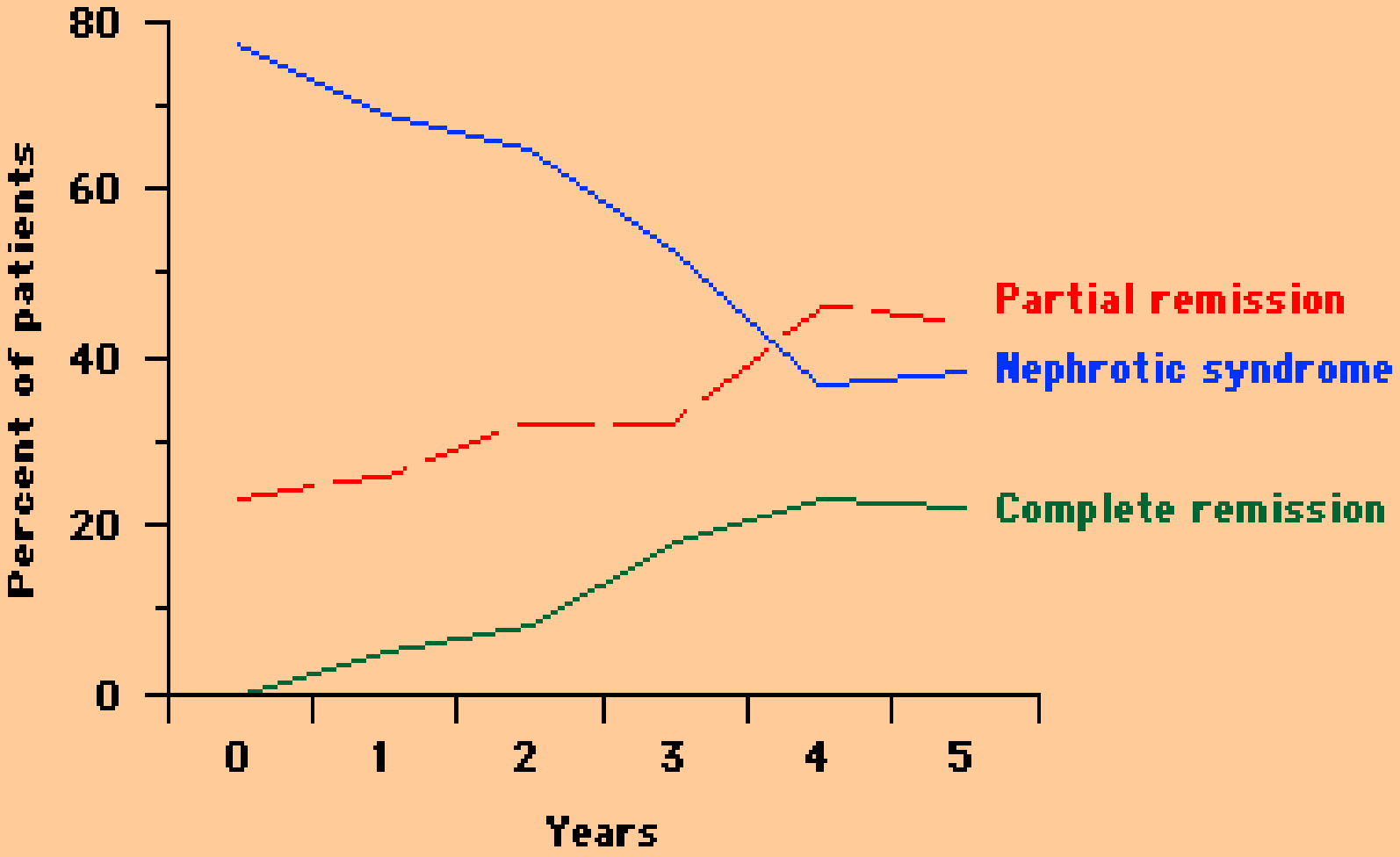
Membranous nephropathy is the most common cause of nephrotic syndrome in adult Caucasian patients

Korbet et al., Am. J. Kidney Dis., 1996, 27: 647 - 651



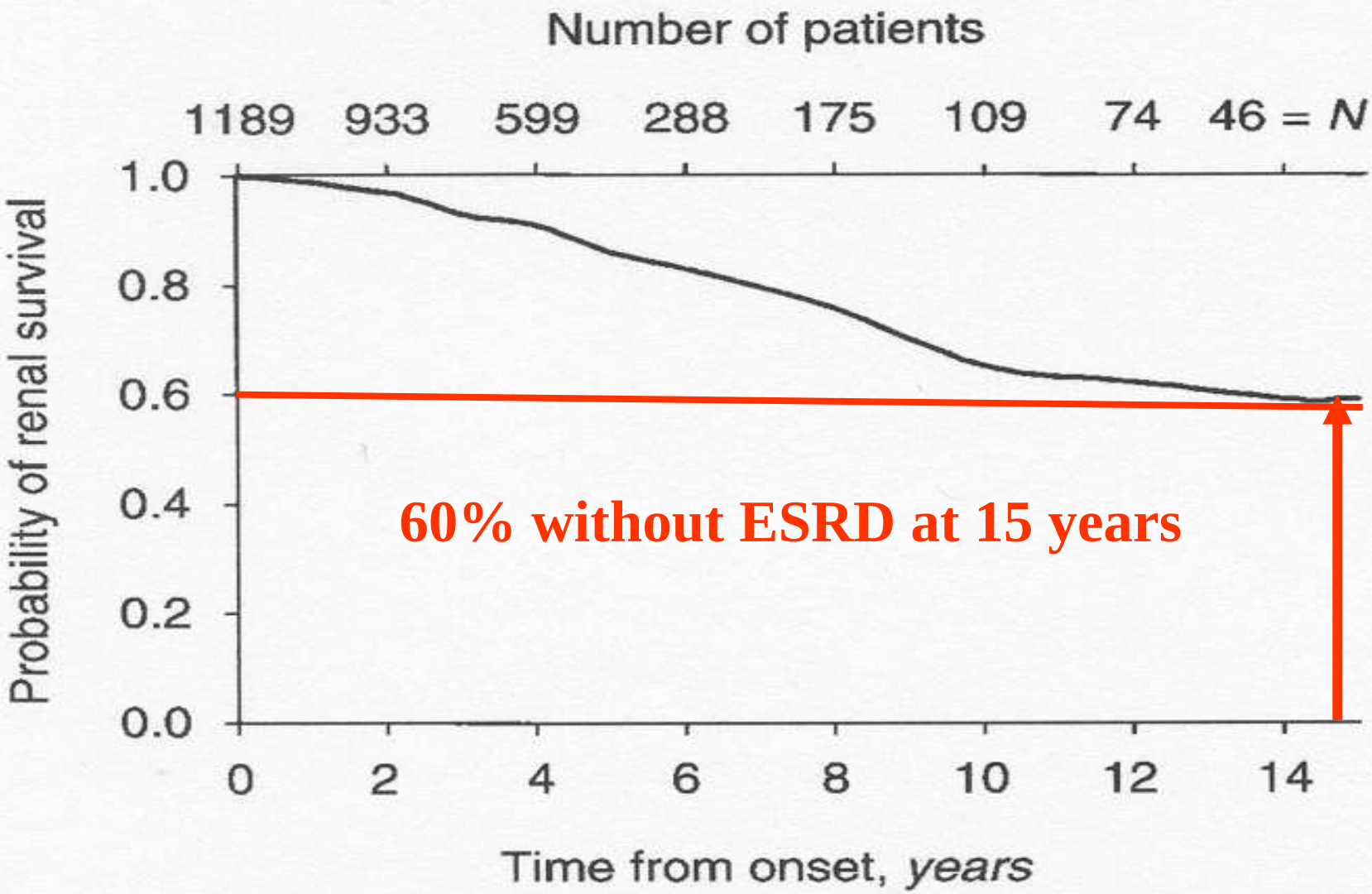
High incidence of remission in untreated MN

Mosconi et al., NEJM, 1993



Probability of renal survival in IMN (review of therapeutic studies)

Hogan et al., Am J Kidney Dis, 1995, 25: 862 - 875



Pathogenesis of IMN

1. Experimental model of IMN – Heymann's nephritis in rats

   - antibodies against megalin

     (not expressed by human podocytes)

2. Antenatal membranous nephropathy in a child of a woman with truncating mutations of MME (metallomembrane endopeptidase) gene

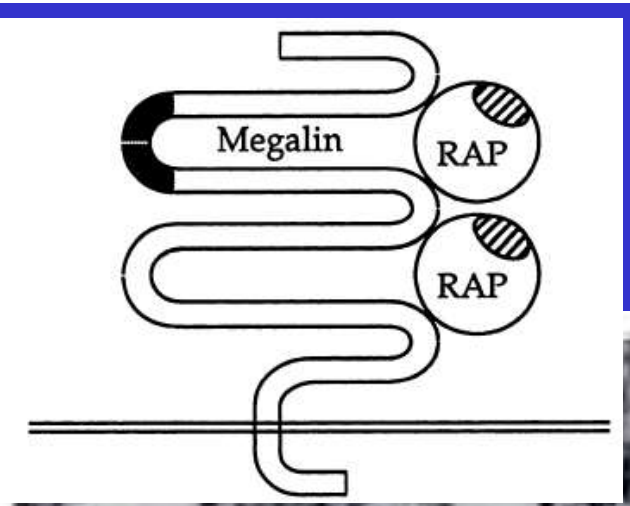
   - alloimmunisation against NEP

3. Common IMN – recently identified autoantibodies to PLA2R

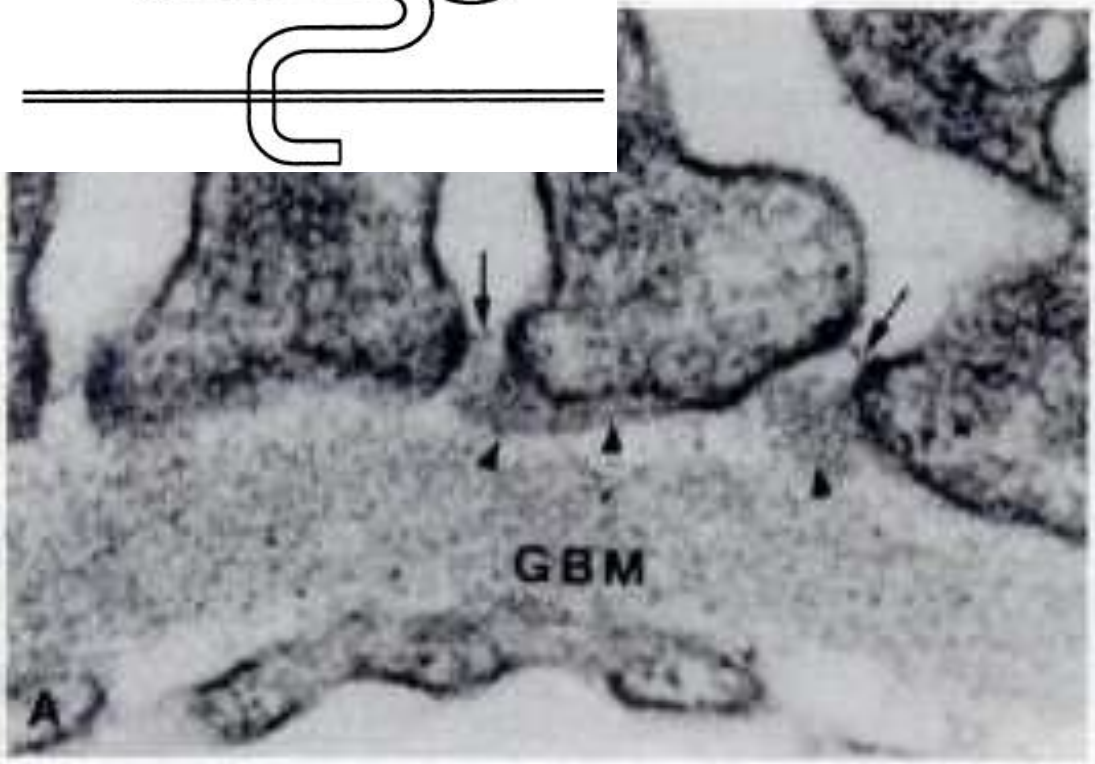
Megalin (gp330) Possesses an Antigenic Epitope Capable of Inducing Passive Heymann Nephritis Independent of the Nephritogenic Epitope in Receptor-Associated Protein[1]

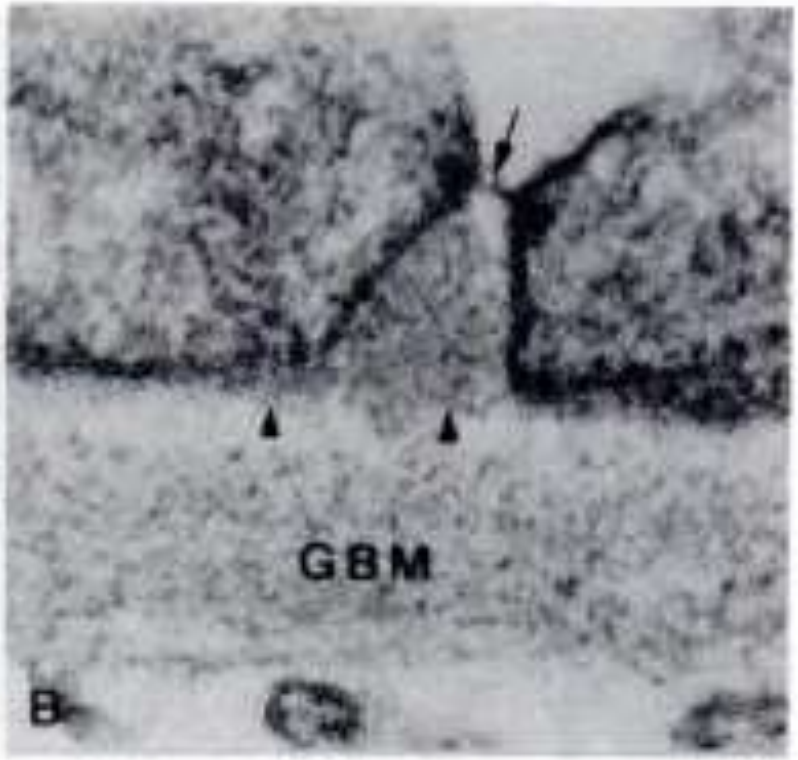
Robert A. Orlando,[2] Dontscho Kerjaschki, and Marilyn Gist Farquhar

(J. Am. Soc. Nephrol. 1995; 6:61–67)



Antimegalin antibodies induced subepithelial deposits in rats



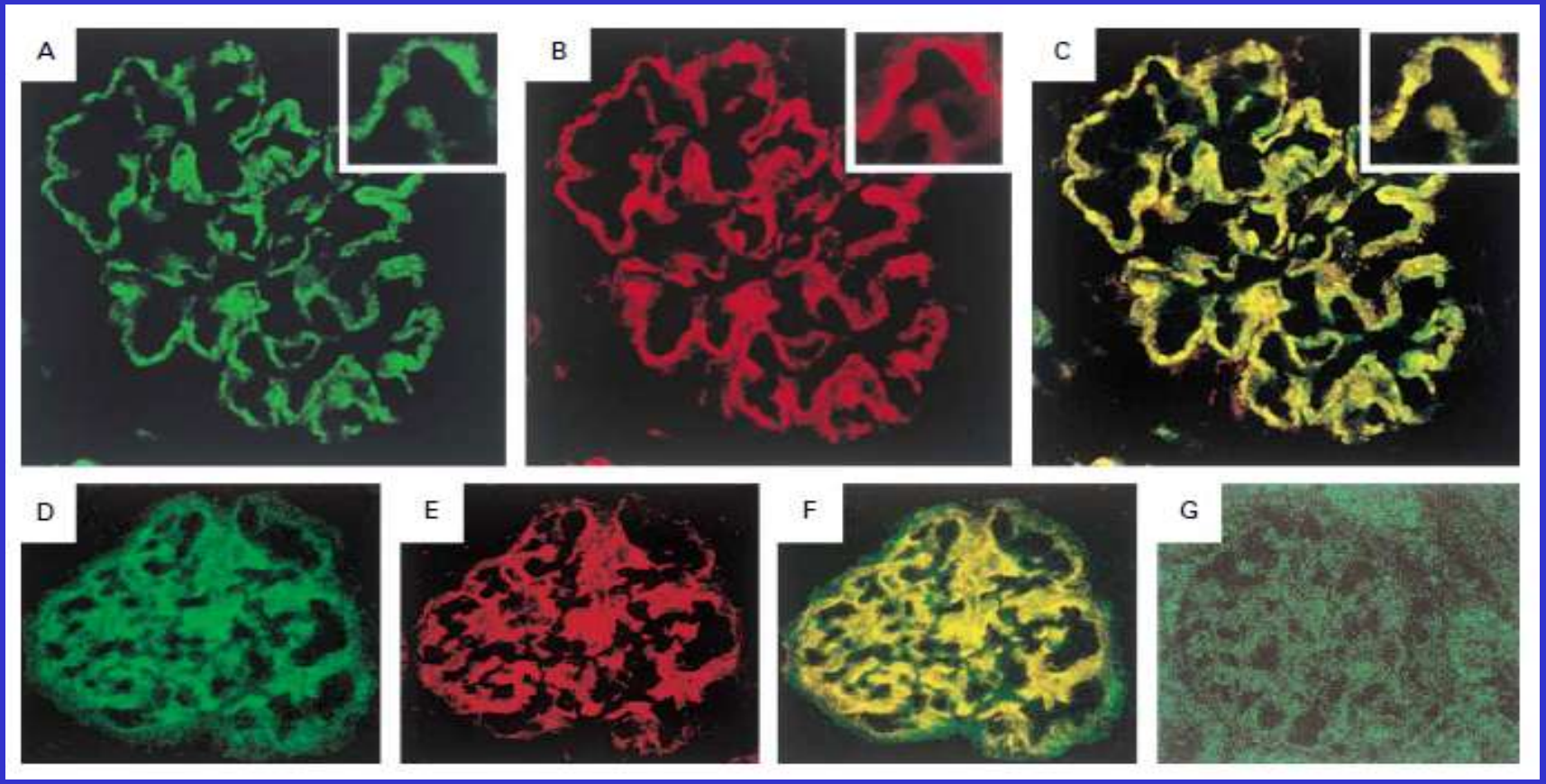


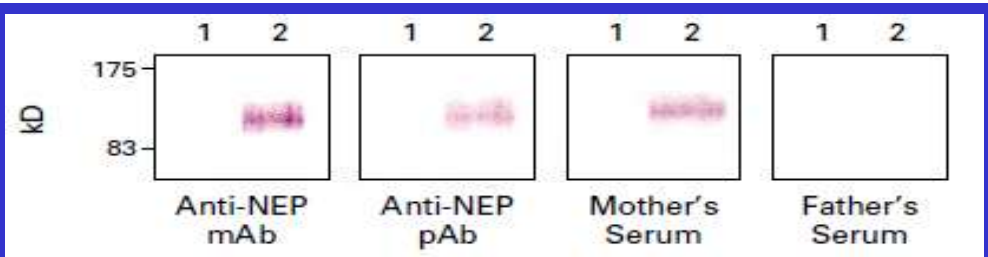
Brief Report

Antenatal Membranous Glomerulonephritis Due to Anti-Neutral Endopeptidase Antibodies

Hanna Debiec, Ph.D., Vincent Guigonis, M.D., Béatrice Mougenot, M.D., Fabrice Decobert, M.D., Jean-Philippe Haymann, M.D., Albert Bensman, M.D., Georges Deschênes, M.D., Ph.D., and Pierre M. Ronco, M.D., Ph.D.

N Engl J Med, Vol. 346, No. 26 · June 27, 2002



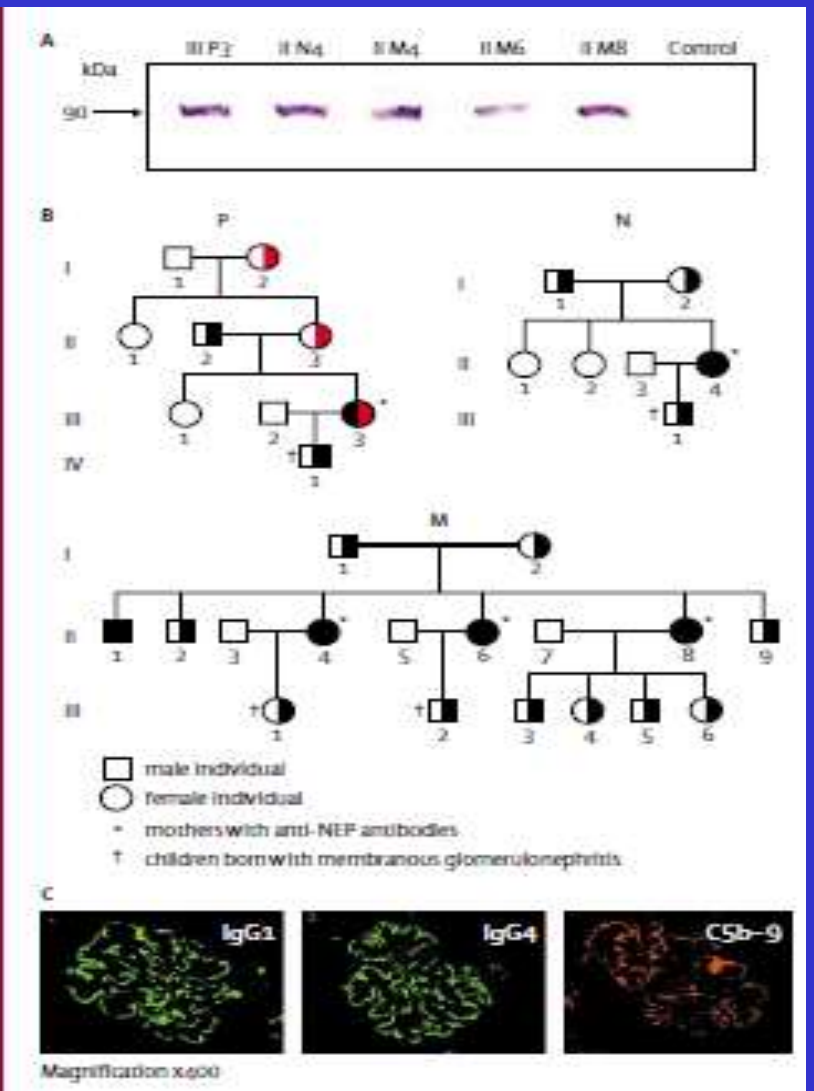


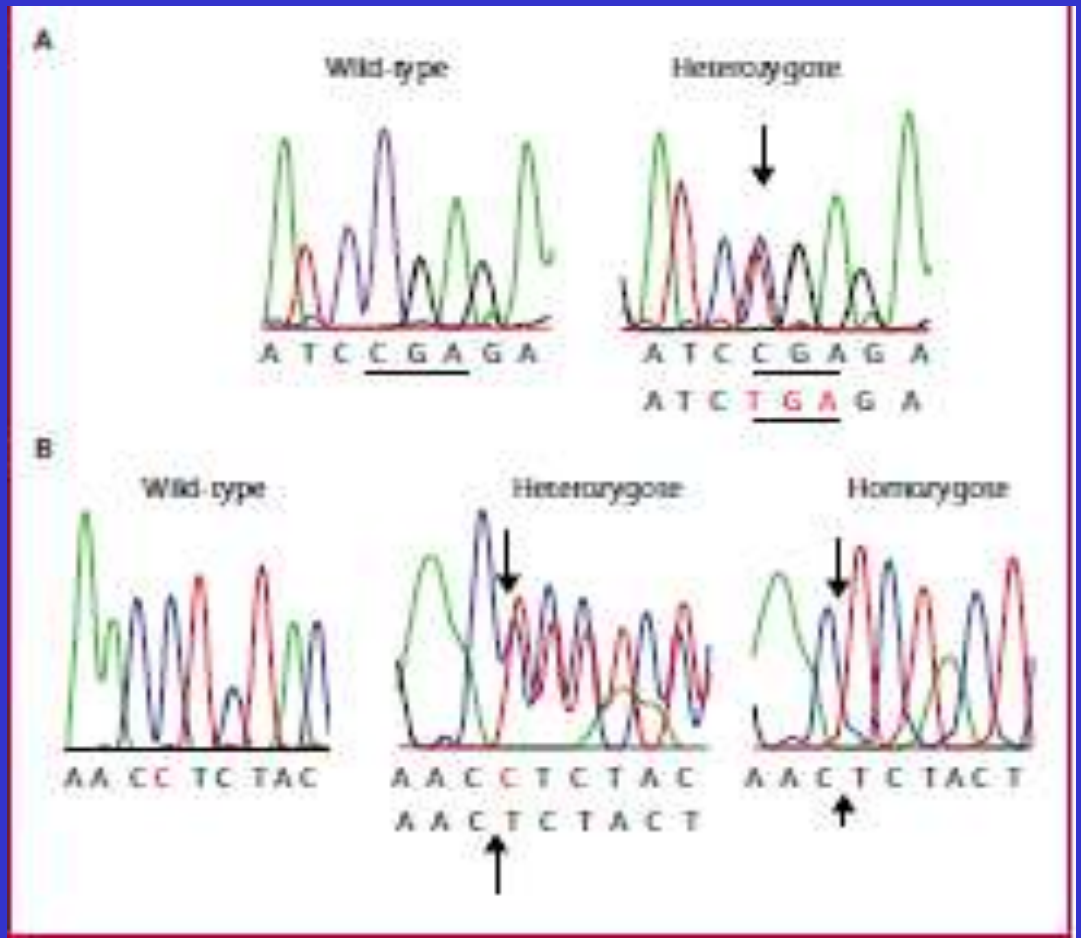
Role of truncating mutations in *MME* gene in fetomaternal alloimmunisation and antenatal glomerulopathies

Lancet 2004; 364: 1252–59
See Comment page 1194

Hanna Debiec, Jeroen Nauta, Florence Coulet, Mirjam van der Burg, Vincent Guigonis, Thierry Schurmans, Emile de Heer, Florent Soubrier, Françoise Janssen, Pierre Ronco

Neonatal MN caused by alloimunisation against NEP

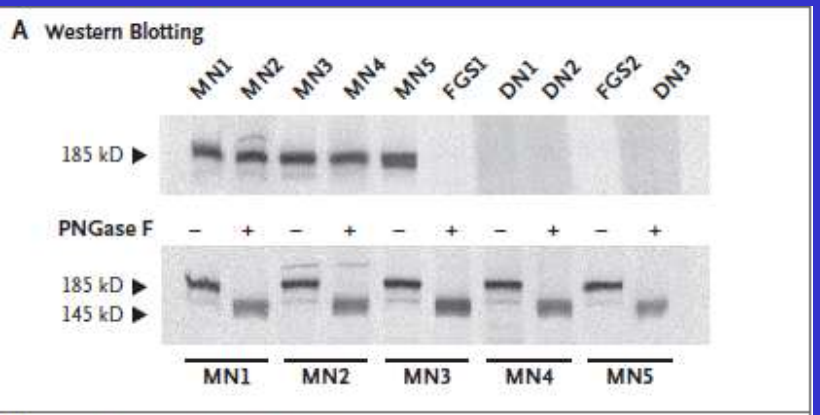


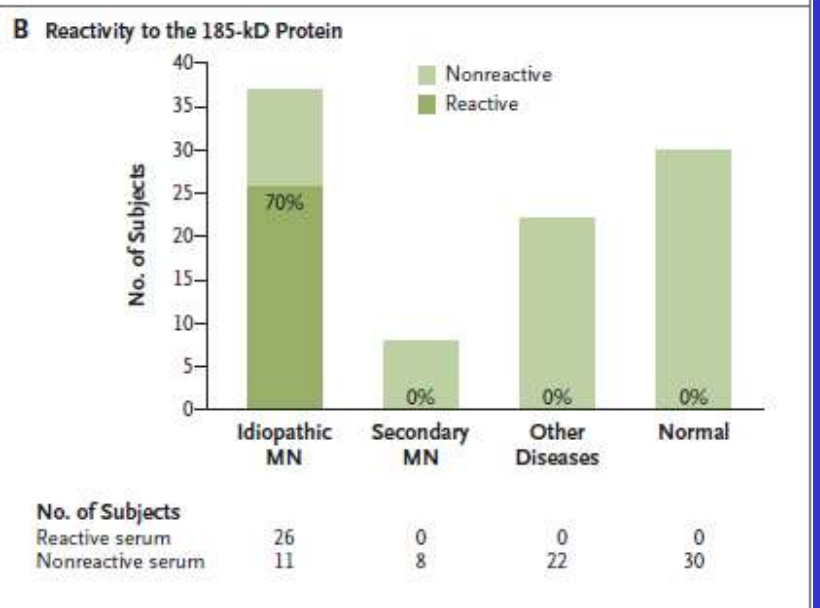


M-Type Phospholipase A_2 Receptor as Target Antigen in Idiopathic Membranous Nephropathy

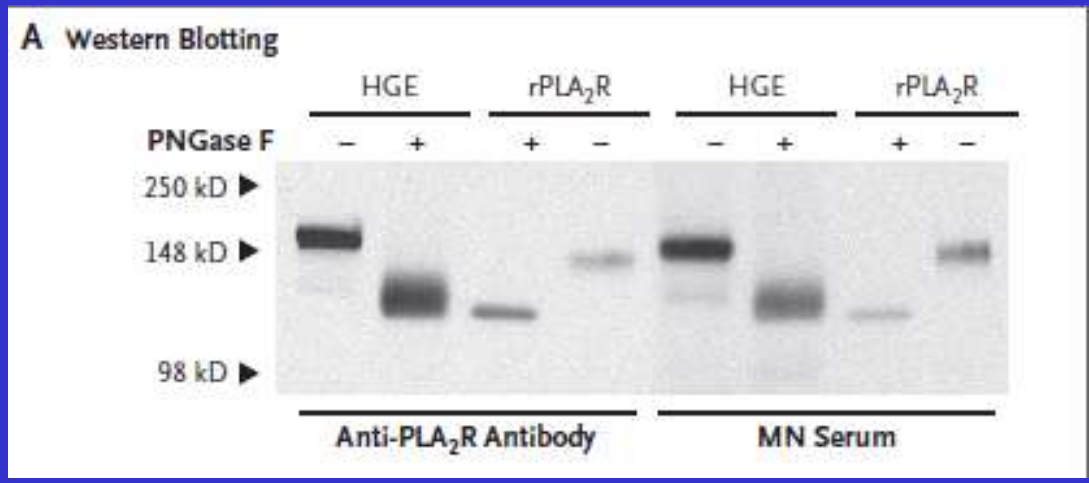
Laurence H. Beck, Jr., M.D., Ph.D., Ramon G.B. Bonegio, M.D., Gérard Lambeau, Ph.D., David M. Beck, B.A., David W. Powell, Ph.D., Timothy D. Cummins, M.S., Jon B. Klein, M.D., Ph.D., and David J. Salant, M.D.

N Engl J Med 2009;361:11-21.





Sera from pts with MN reacted with 185 kD protein identified as M-type phospholipase A2 receptor



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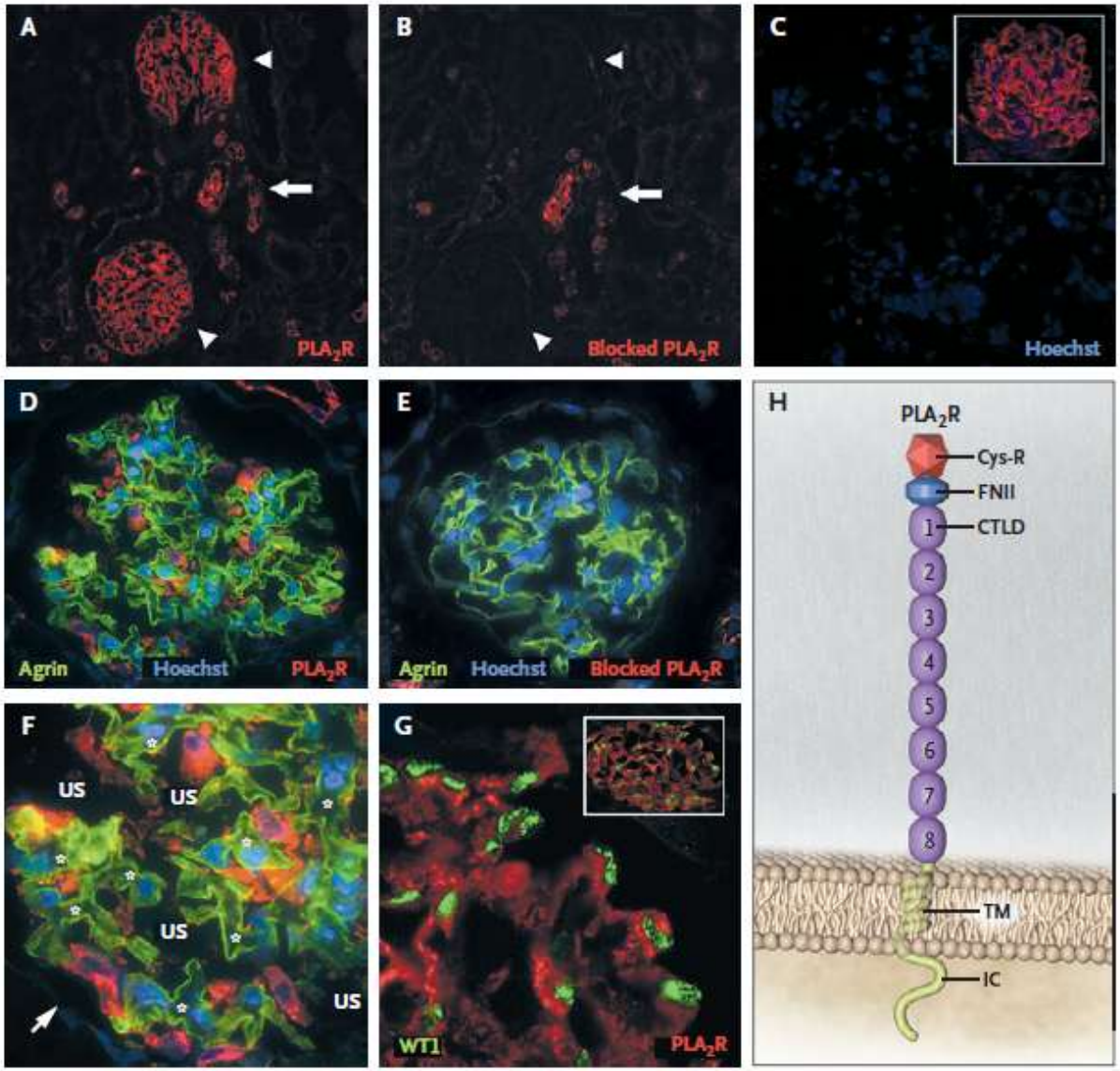
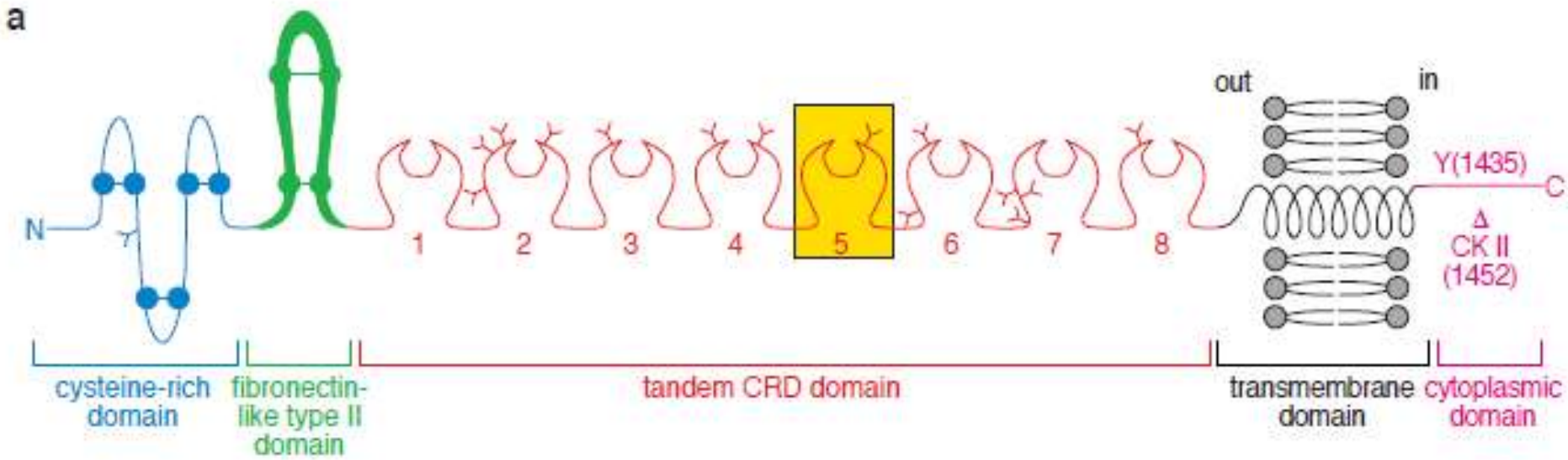


Antibodies were colocalized with GBM and podocytes


a
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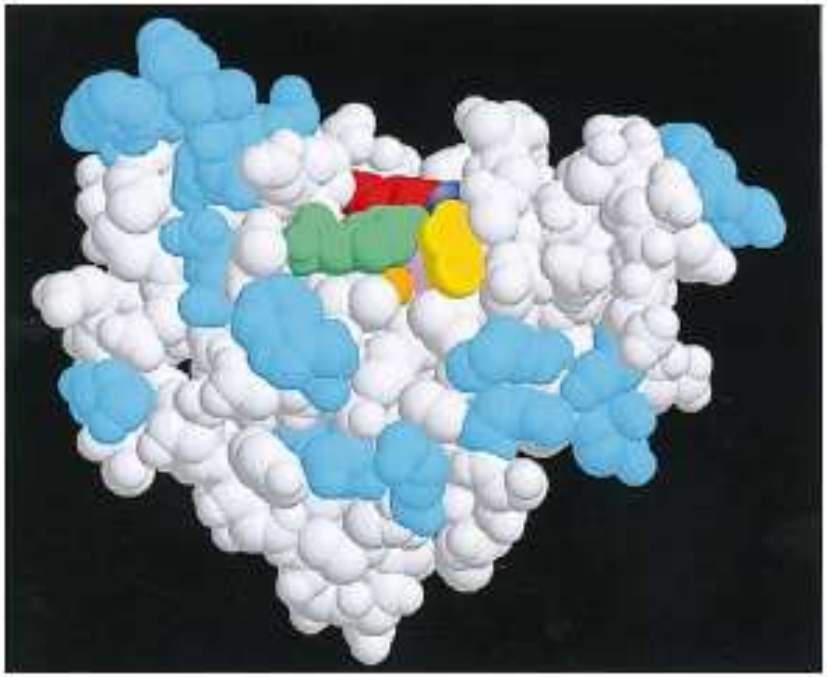
fibronectin-like type II domain
tandem CRD domain
transmembrane domain
cytoplasmic domain

b



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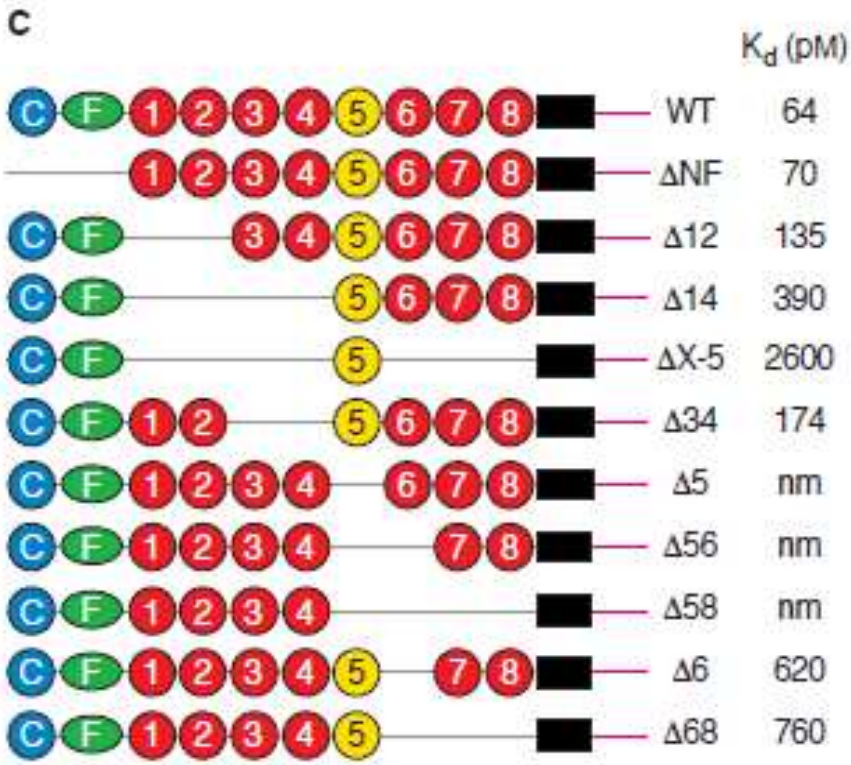
K_d (pM)
WT 64
ΔNF 70
Δ12 135
Δ14 390
ΔX-5 2600
Δ34 174
Δ5 nm
Δ56 nm
Δ58 nm
Δ6 620
Δ68 760

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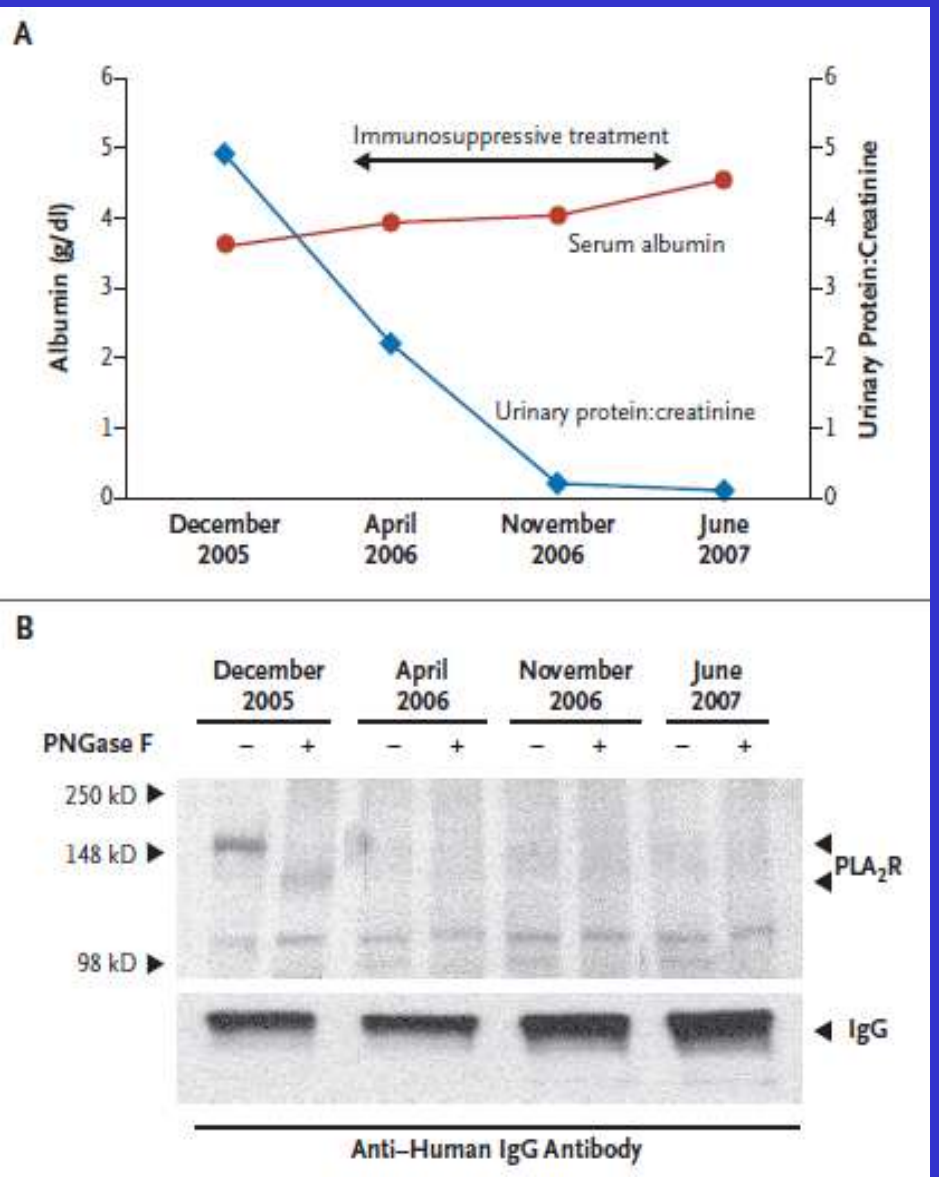


Autoantibodies disappeared after immunosuppressive treatment in parallel with the decrease of proteinuria

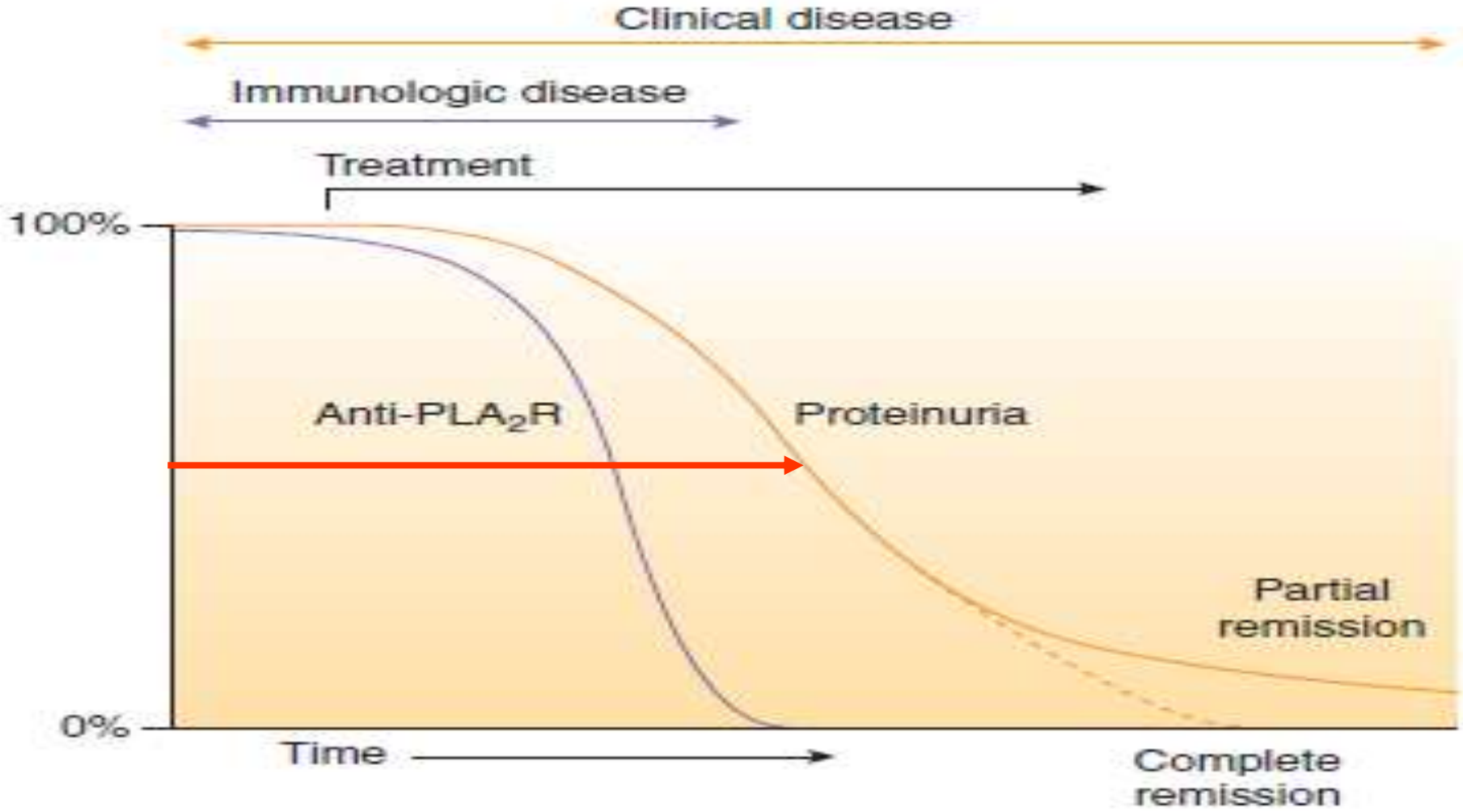
Antibodies could enhance diagnostics and could be useful for monitoring of the activity of MN and the effect of IST

Membranous nephropathy: recent travels and new roads ahead

Kidney International (2010) **77,** 765–770

Laurence H. Beck Jr[1] and David J. Salant[1]

Disappearance of anti-PLAR2 Ab may precede the complete remission of IMN



Membranous nephropathy: recent travels and new roads ahead

Kidney International (2010) **77,** 765–770

Laurence H. Beck Jr[1] and David J. Salant[1]

Table 1 | Causes of idiopathic and secondary membranous nephropathy (MN)

Idiopathic
Anti-phospholipase A2 receptor (75%)
Antigen still unknown or simply inactive (25%)
Secondary (causative antigen still unknown)
Systemic lupus erythematosus
Hepatitis B
Malignancy
Other causes
Alloimmune
Fetomaternal alloimmunization to neutral endopeptidase
De novo MN post-renal transplantation (?)
MN post-allogeneic stem cell transplantation (?)

Anti-Phospholipase A_2 Receptor Antibodies Correlate with Clinical Status in Idiopathic Membranous Nephropathy

CJASN ePress. Published on April 7, 2011 as doi: 10.2215/CJN.07210810

Julia M. Hofstra, Laurence H. Beck, Jr.,† David M. Beck,† Jack F. Wetzels,* and David J. Salant‡*

Anti-PLA2R antibodies were positive in 78% out of 18 pts with IMN and correlated with baseline proteinuria

Table 1. Baseline characteristics (n = 18)

Gender (male/female)	14/4
Age (years)	51 ± 10
sCreat (μmol/l)	122 ± 44
sAlbumin (g/dl)	2.6 ± 0.7
Proteinuria (g/d)	10.2 ± 4.7
β2m excretion (ng/min)	1786 (99 to 62000)
IgG excretion (mg/d)	249 (21 to 3082)
eGFR (ml/min per 1.73 m^2)	50 (25 to 104)
sβ2m (mg/l)	3.66 (1.63 to 12.48)
sIgG (g/l)	4.34 (1.85–13.35)
Selectivity index	0.24 ± 0.12
anti-PLA_2R (densitometric units)	10,042 (0–30115)

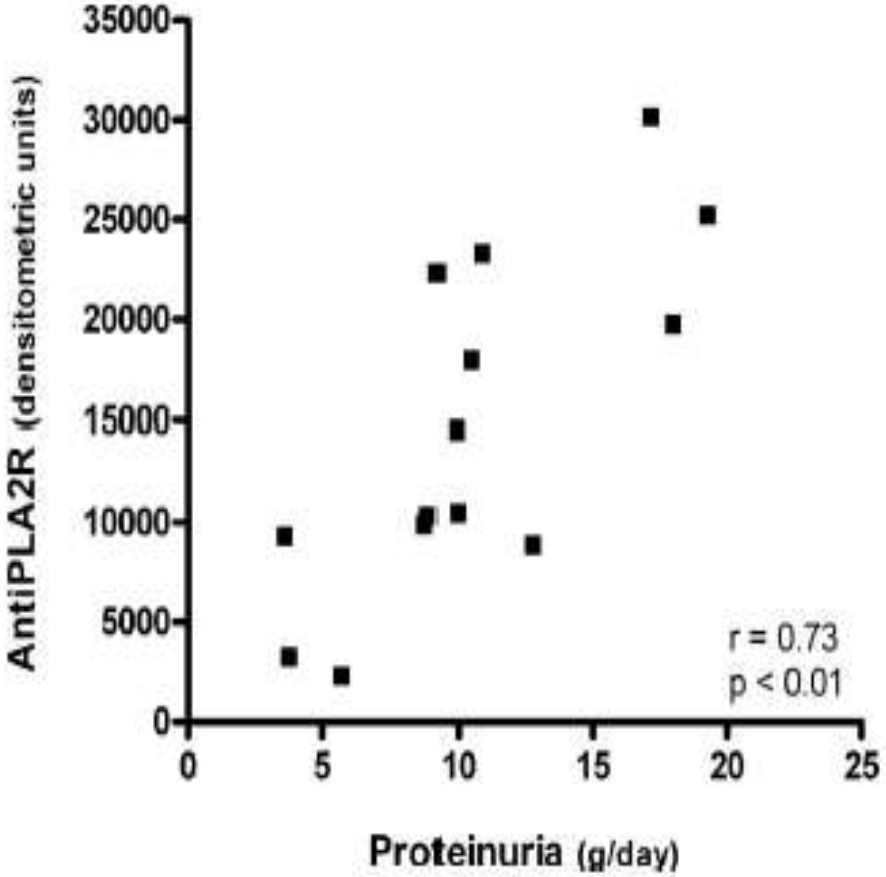


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Table 2. Clinical course in anti-PLA$_2$R positive patients with remission of proteinuria during follow-up (n = 13)

	Presentation				Remission					Relapse			
Patient	Proteinuria (g/d)	eGFR (ml/min per 1.73 m^2)	aPLA$_2$R Level (dens. units)	Time to Remission (months)	Proteinuria (g/d)	eGFR (ml/min per 1.73 m^2)	aPLA$_2$R Level (dens. units)	Type of Remission	Treatment	Time to Relapse (months)	Proteinuria (g/d)	eGFR (ml/min per 1.73 m^2)	aPLA$_2$R Level (dens. units)
1	3.8	71	3203	24	2.0	77	438	Spont.					
2	3.6	62	9251	15	0.2	62	0	Spont.					
3	5.8	83	2236	18	2.1	90	877	Spont.					
4	10.5	25	17927	13	0.4	48	0	Ther.	MMF + P 12 months				
5	12.8	51	8802	19	0.4	96	135	Ther.	MMF + P 12 months				
6	8.8	95	9823	16[b]	1.6	93	ND[b]	Spont.		67	8.3	95	3780
7	8.9	104	10260	45	1.5	86	8555	Spont.		51	6.6	99	7416
8	12.5	66	25116[a]	20	0.3	83	0	Ther.	CP + P 12 months	75	20.2	71	19757
9	10.0	44	14510	18	0.7	67	399	Ther.	CP + P 12 months	104	7.1	50	9491
10	18.0	64	19721	28	1.8	57	341	Ther.	CP + P 12 months	69	9.7	50	18373
11	10.0	34	10379	11	0.1	61	0	Ther	CP + P 12 months	44	7.9	64	9491
12	17.2	31	30115	14	0.8	86	0	Ther.	CP + P 12 months	19	10.0	55	8769
13	10.9	27	23235	23	0.4	35	0	Ther.	CP + P 12 months	65	4.9	31	6934

eGFR, estimated GFR by MDRD6 formula; aPLA$_2$R, anti-PLA$_2$R; dens. units, densitometric units; Time to Remission, time between presentation and onset of remission; Time to Relapse, time between onset of remission and onset of relapse; Spont., spontaneous remission; Ther., therapy-induced remission; MMF, myco-phenolate mofetil; P, prednisone; CP, cyclophosphamide.

[a]Sample 4 months after presentation: in the initial sample anti-PLA$_2$R was not detected (see text).

[b]There is no sample available for this remission (see text).

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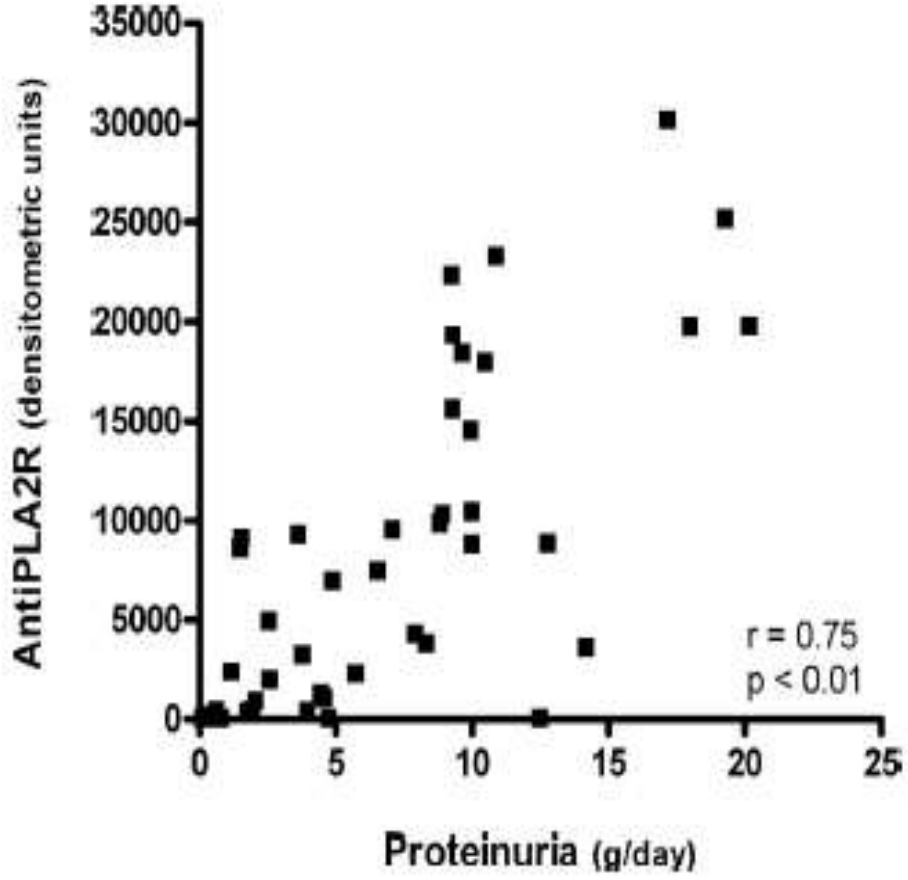
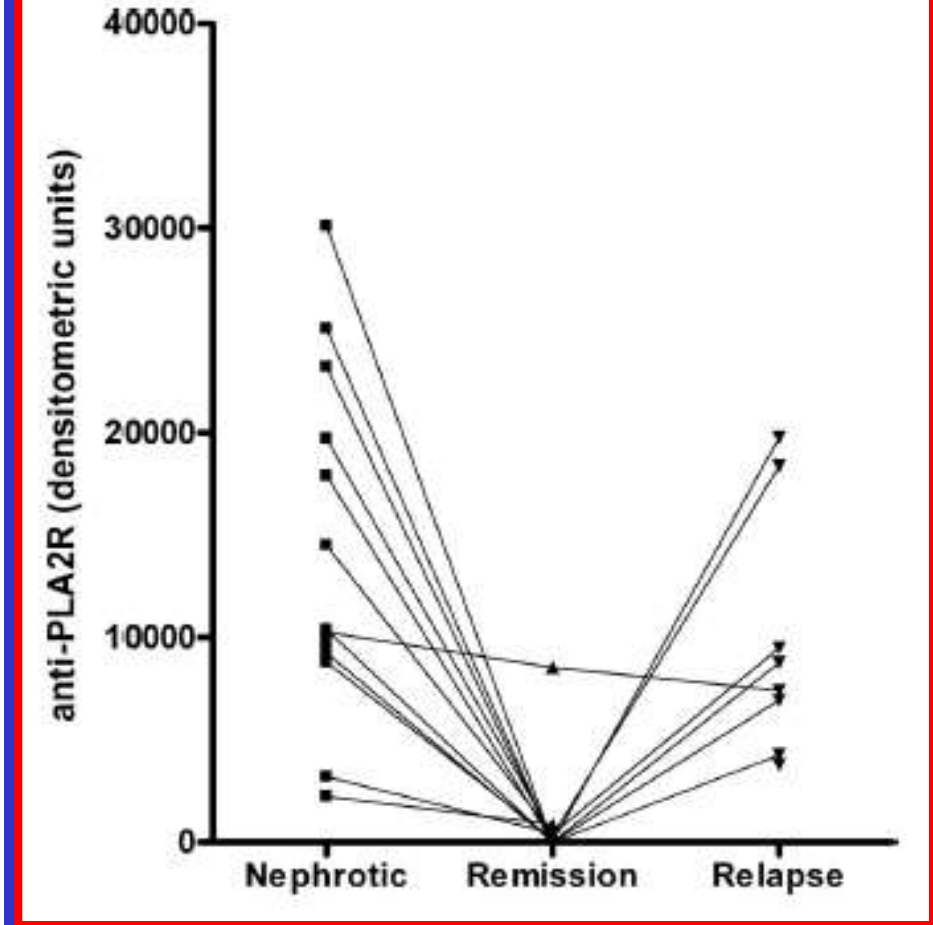
Anti-PLA2R antibodies correlated with Pu during the disease



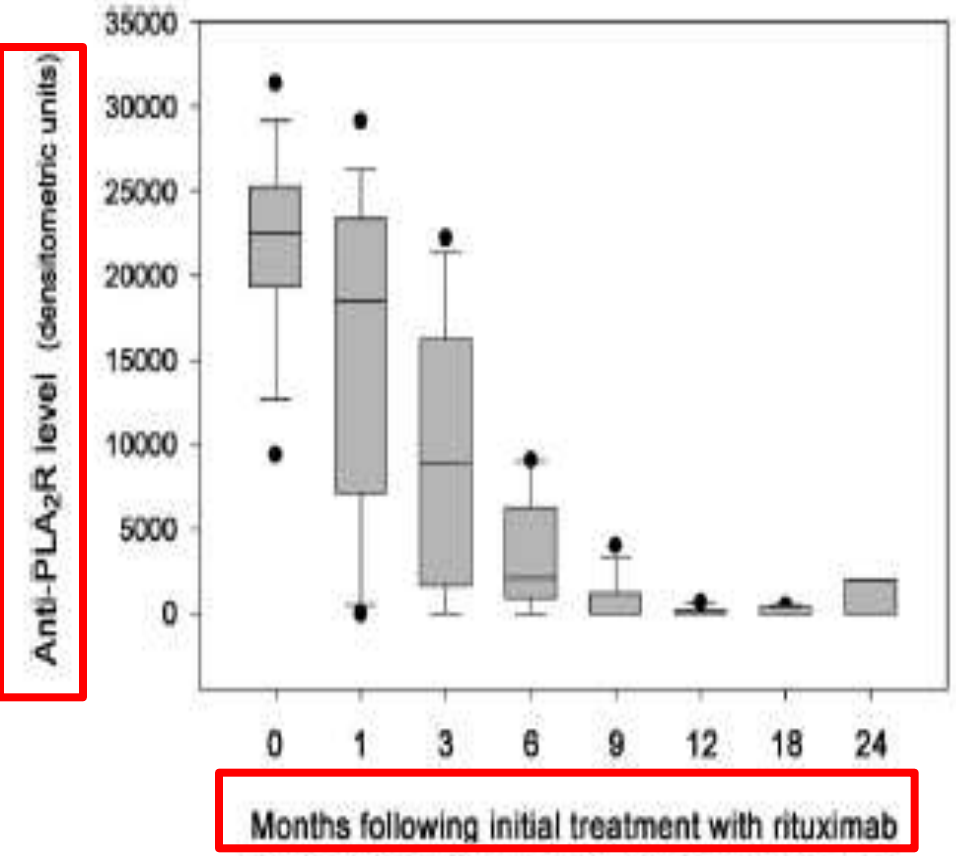


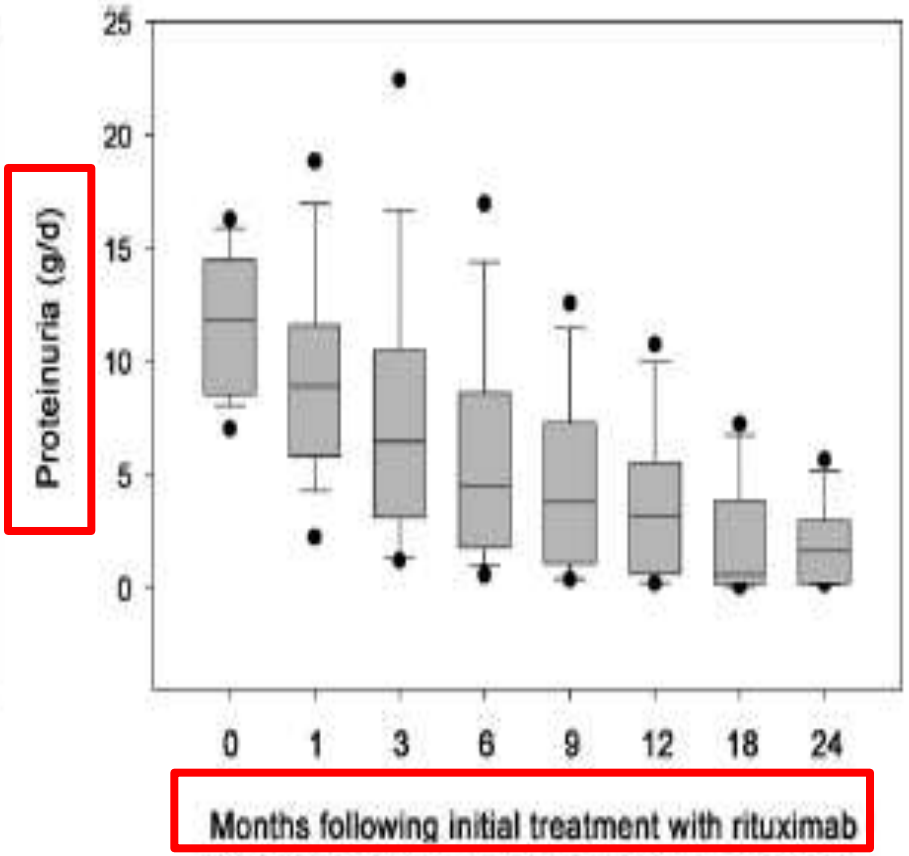
Rituximab-Induced Depletion of Anti-PLA$_2$R Autoantibodies Predicts Response in Membranous Nephropathy

J Am Soc Nephrol 22: 1543–1550, 2011.

Laurence H. Beck, Jr.,* Fernando C. Fervenza,† David M. Beck,* Ramon G.B. Bonegio,* Fahim A. Malik,* Stephen B. Erickson,† Fernando G. Cosio,† Daniel C. Cattran,‡ and David J. Salant*

Anti-PLA2R antibodies were positive in 71% out of 35 pts with IMN and declined or disappeared within 12 months in 68% of them





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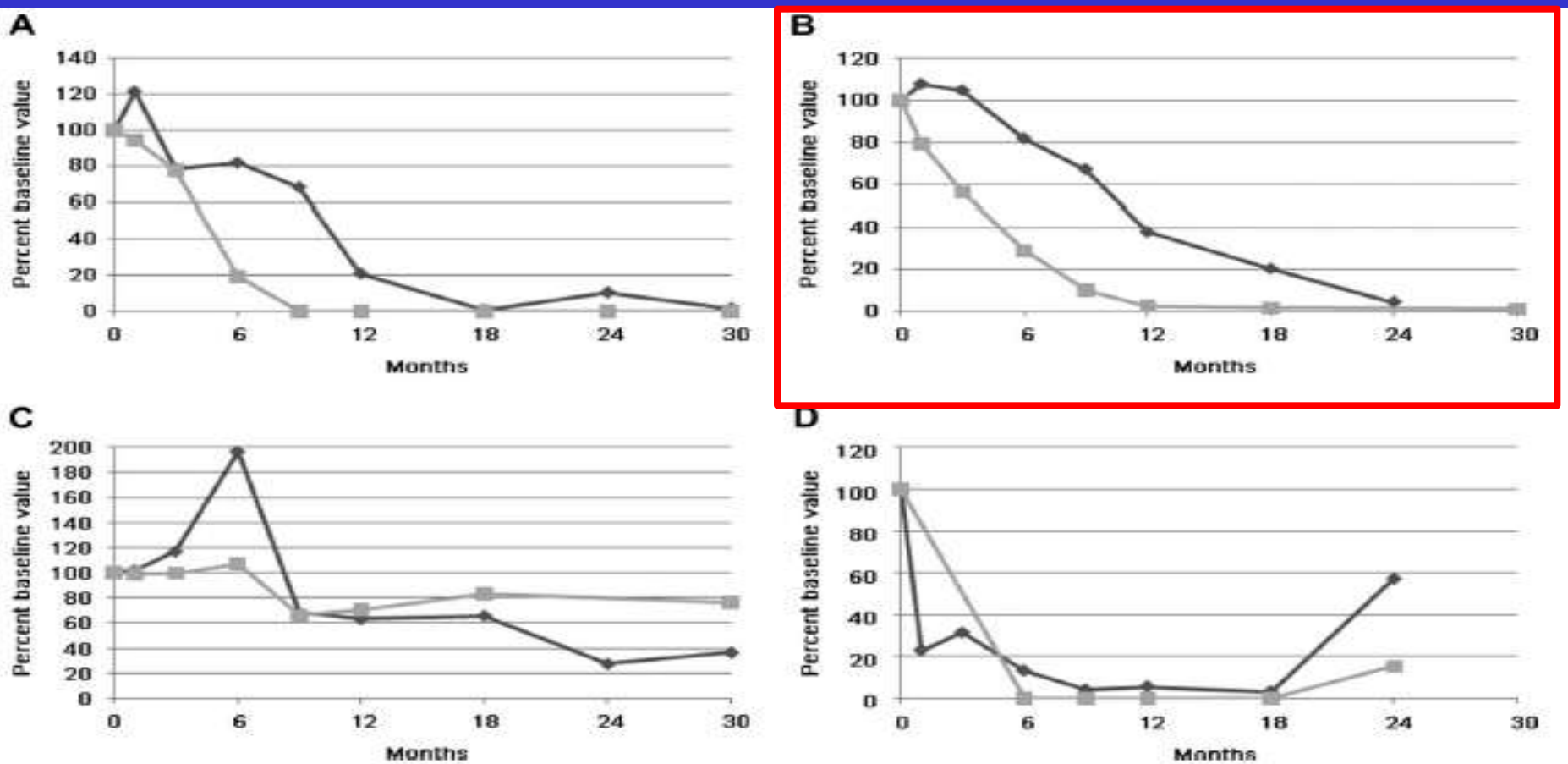
Decrease of anti-PLA2R preceded decrease of Pu in some, but not all pts with IMN treated by RTX



Anti-Phospholipase A2 Receptor Antibody in Membranous Nephropathy

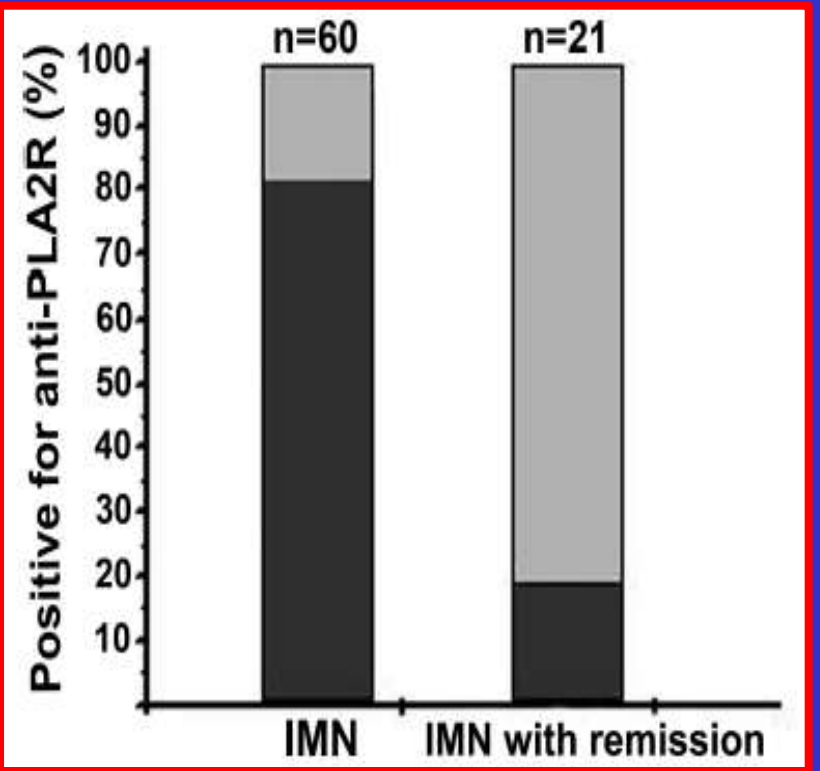
Weisong Qin,* Laurence H. Beck, Jr.,† Caihong Zeng,* Zhaohong Chen,* Shijun Li,* Ke Zuo,* David J. Salant,† and Zhihong Liu*

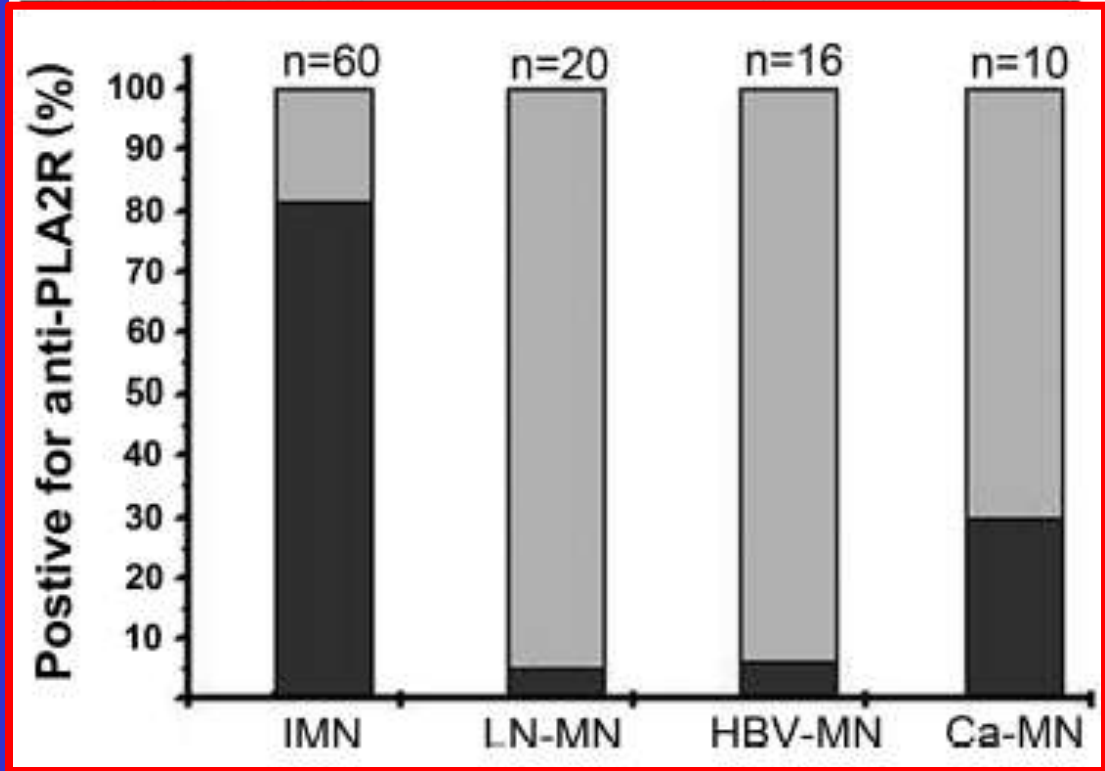
J Am Soc Nephrol 22: ●●●–●●●, 2011. doi: 10.1681/ASN.2010090967

Anti-PLA2R Ab positive in 80% of pts with IMN at presentation and 20% in remission

Table 1. Anti-PLA2R in Chinese patients with membranous nephropathy

	n	Anti-PLA2R	%
Idiopathic MN	60	49	81.7%
Lupus MN	20	1	5.0%
HBV-associated MN	16	1	6.3%
Tumor-associated MN	10	3	30%





PLA_2R Autoantibodies and PLA_2R Glomerular Deposits in Membranous Nephropathy

N ENGL J MED 364;7 NEJM.ORG FEBRUARY 17, 2011

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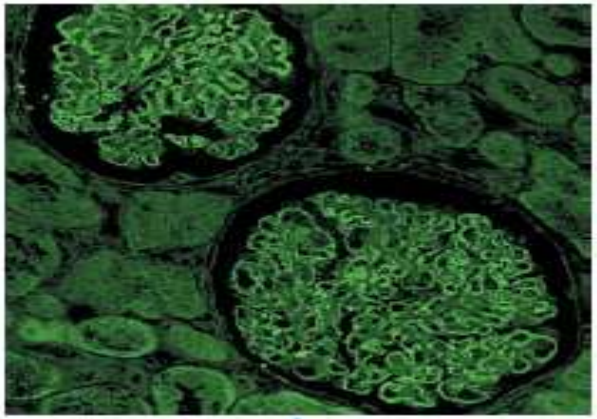
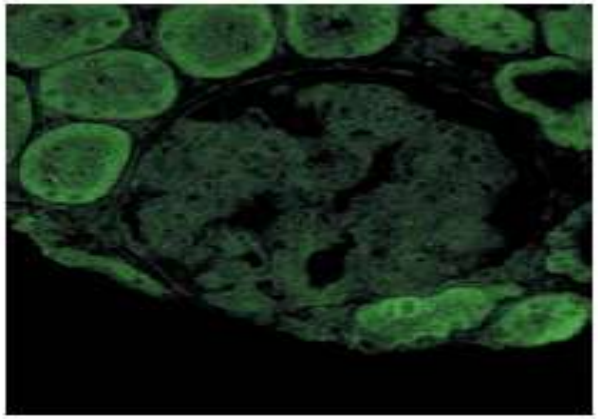
Deposition of anti-PLA2R antibodies in glomeruli documented also in some pts with negative anti-PLA2R in sera

N=21



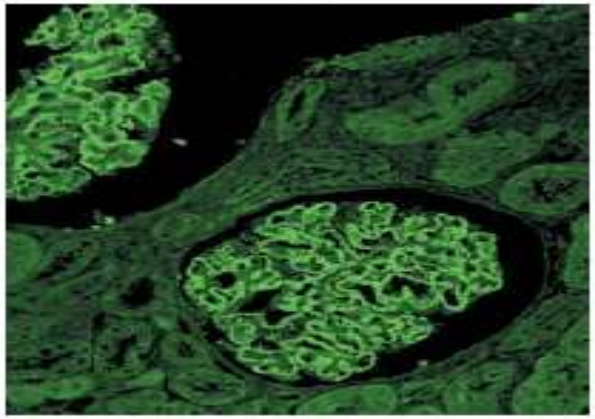
Serum anti-PLA_2R positive

N=8

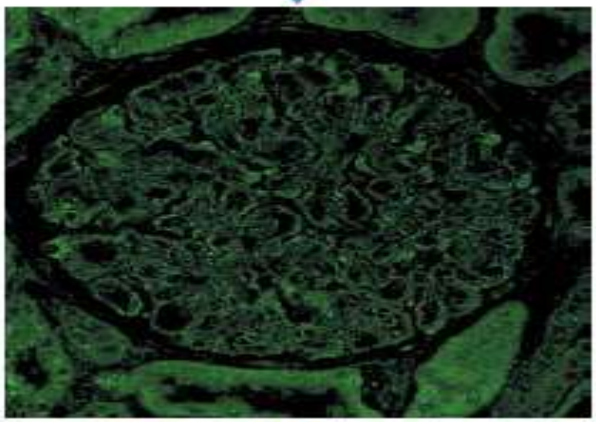


Serum anti-PLA_2R negative

N=10



Serum anti-PLA_2R negative



N=3

	PLA_2R	
No. of Patients	Serum Reactivity	Biopsy
21	+	+
3	+	–
8	–	–
10	–	+
42	+24	+31
	57%	74%

Risk HLA-DQA1 and PLA_2R1 Alleles in Idiopathic Membranous Nephropathy

N Engl J Med 2011;364:616-26.

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In GWAS of 556 pts with IMN alleles of HLA-DQA1 and PLA2R1 were associated with susceptibility to IMN

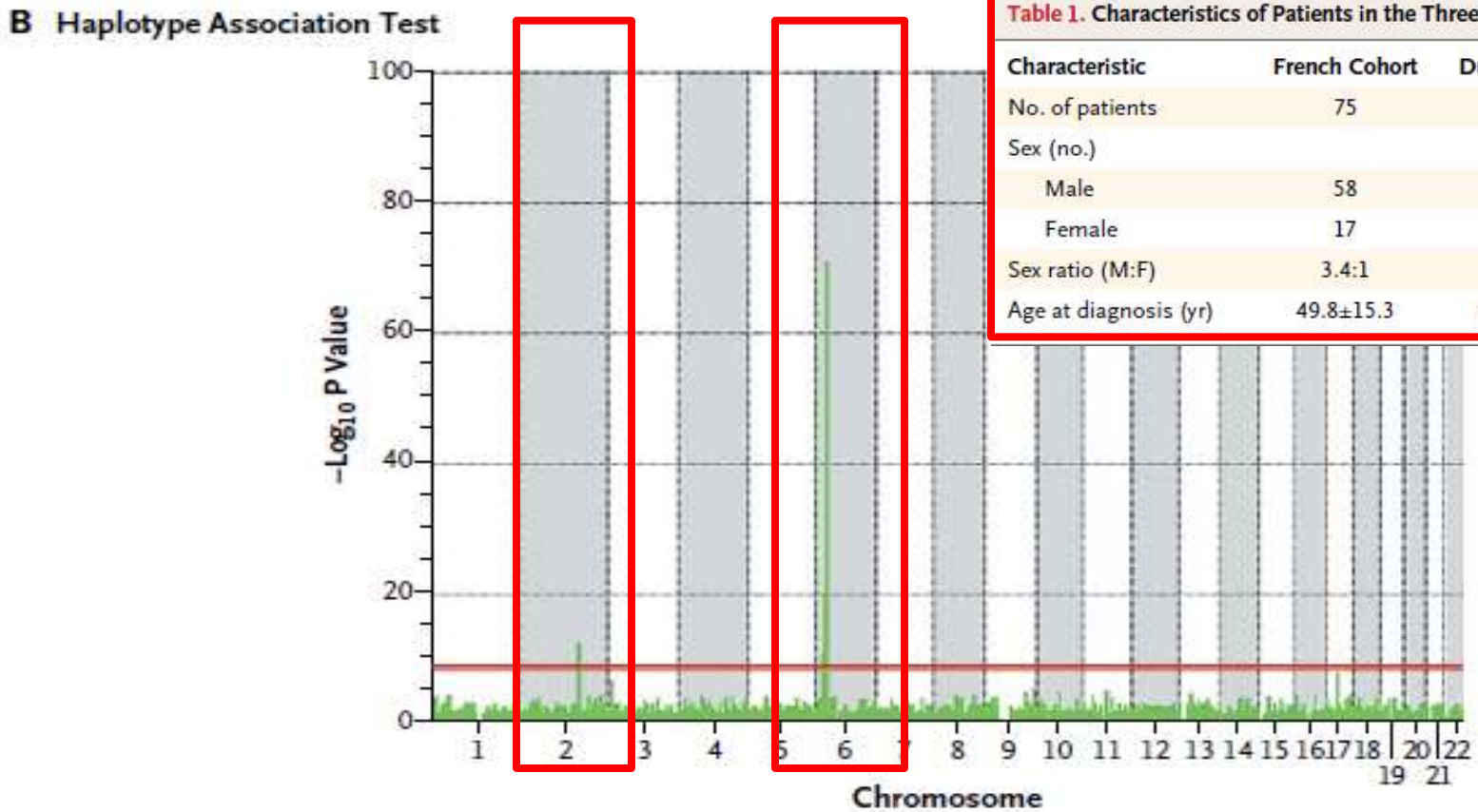

Table 1. Characteristics of Patients in the Three Study Cohorts.*

Characteristic	French Cohort	Dutch Cohort	British Cohort
No. of patients	75	146	335
Sex (no.)			
Male	58	109	231
Female	17	37	104
Sex ratio (M:F)	3.4:1	2.9:1	2.2:1
Age at diagnosis (yr)	49.8±15.3	51.8±14.2	52.5±13.3

Table 2. Results of Genomewide Association Studies in the Three Study Groups and the Joint Study, According to Single-Nucleotide Polymorphism Characteristics.*

Variable	Single-Nucleotide Polymorphism Characteristics	
	Chromosome 6, rs2187668 (HLA-DQA1)	Chromosome 2, rs4664308 (*PLA2R1*)
French study		
Odds ratio (95% CI)	4.48 (2.68–7.50)	1.87 (1.20–2.92)
Minor allele frequency (%)		
Patients	31.3	23.3
Controls	9.2	36.3
P value	1.8×10^{-9}	5.1×10^{-3}
Dutch study		
Odds ratio (95% CI)	3.76 (2.92–4.86)	2.27 (1.73–2.97)
Minor allele frequency (%)		
Patients	37.0	26.0
Controls	13.5	44.4
P value	5.6×10^{-27}	1.0×10^{-9}
British study		
Odds ratio (95% CI)	5.33 (4.04–7.02)	2.10 (1.67–2.64)
Minor allele frequency (%)		
Patients	41.9	25.3
Controls	11.9	41.6
P value	5.2×10^{-36}	2.1×10^{-10}
Joint study		
Odds ratio (95% CI)	4.32 (3.73–5.01)	2.28 (1.96–2.64)
Minor allele frequency (%)		
Patients	39.2	25.2
Controls	13.0	43.4
P value	8.0×10^{-93}	8.6×10^{-29}

Risk HLA-DQA1 and PLA_2R1 Alleles in Idiopathic Membranous Nephropathy

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Subjects with both risk alleles in both HLA-DQA1 nad PLA2R1 had almost 80 times higher risk of IMN

Table 3. Odds Ratios for Idiopathic Membranous Nephropathy, According to Single-Nucleotide Polymorphism (SNP) and Genotype Combinations.*

SNP rs2187668 (HLA-DQA1)	SNP rs4664308 (*PLA2R1*)		
	GG	GA	AA
GG			
No. of cases/total no. of subjects	14/354	79/944	97/659
Odds ratio (95% CI)	1.00	2.22 (1.24–3.97)	4.19 (2.36–7.46)
GA			
No. of cases/total no. of subjects	23/115	94/363	178/348
Odds ratio (95% CI)	6.07 (3.01–12.27)	8.49 (4.73–15.22)	25.43 (14.32–45.16)
AA			
No. of cases/total no. of subjects	5/11	23/41	42/55
Odds ratio (95% CI)	20.24 (5.51–74.38)	31.03 (13.72–70.19)	78.46 (34.55–178.17)

Conclusions

1. podocytopenia is deleterious in terms of renal survival
2. identification of the mutated genes for the podocyte proteins enhanced our understanding of podocyte function
3. impaired podocyte signaling may cause both reversible and irreversible podocyte damage
4. damage to the podocytes may be effectively treated only by drugs which interfere with podocyte signaling
5. anti-PLA2R Ab may enhance an early and non-invasive diagnosis of IMN and help with the monitoring of the immunosuppressive treatment