Mekanismer bakom FSGS

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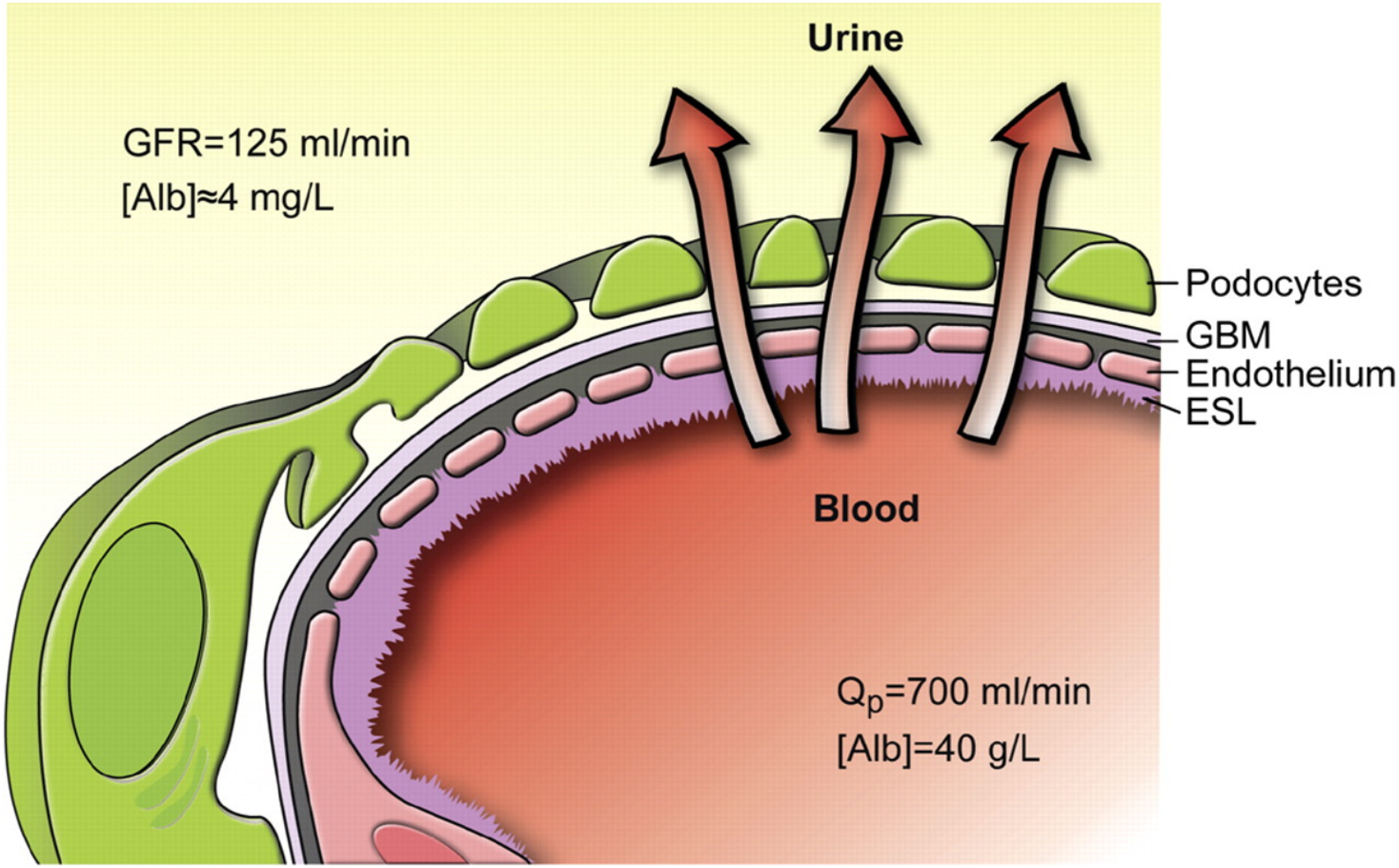
Icahn School of Medicine at Mount Sinai, New York, 2011-

Njurmedicinskt vårmöte i Trollhättan, maj 2014

Schematic drawing of the four components of the glomerular barrier



Haraldsson, Nyström & Deen. Properties of the glomerular barrier and mechanisms of proteinuria. Physiol. Rev. 88: 451-487 2008;

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Podocyte-enriched genes associated with FSGS in humans

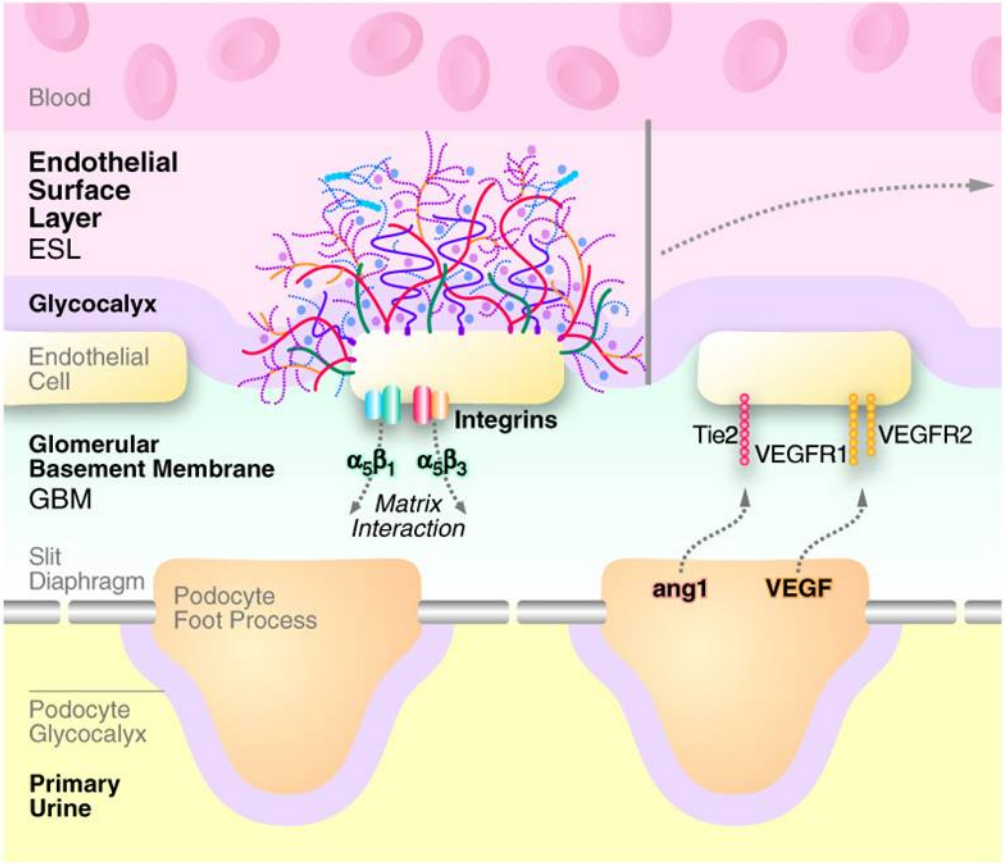
Table 4 | Genes associated with FSGS in humans

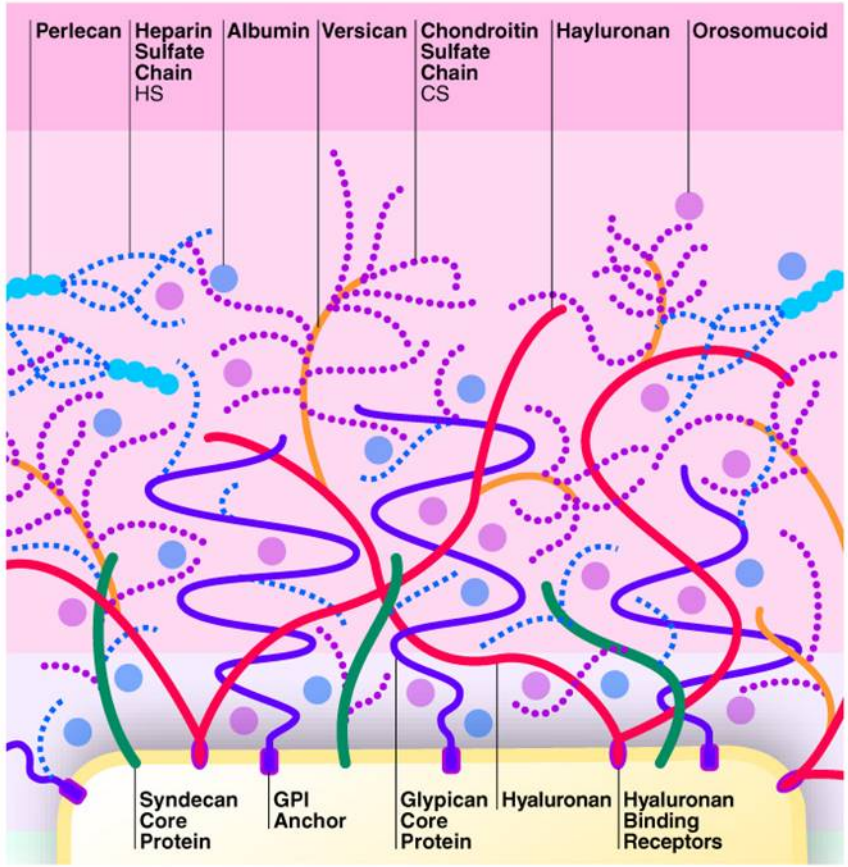
Gene	Location	Gene product	Disease	Inheritance mode	OMIM number
ACTN4	19q13	α-Actinin-4	FSGS type1	AD	603278
NPHS1	19q13	Nephrin	Finnish-type congenital nephropathy, SRNS	AR, sporadic	256300
NPHS2	1q25.32	Podocin	SRNS type 2	AR, sporadic	600995
TRPC6	11q21.22	Short transient receptor potential channel 6	FSGS type 2	AD	603965
CD2AP	6q12	CD2-associated protein	SRNS type 4	AR, AD, sporadic	600995
PLCE1	10q23.24	Phospholipase Cε-1	SRNS type 3	AR	610725
WT1	11p13	Wilms tumour protein	Denys–Drash syndrome, Frasier syndrome, nephrotic syndrome type 4	AD	194080, 136680, 256370
LMX1B	9q34.1	LIM homeobox transcription factor 1β	Nail-patella syndrome	AD	161200
tRNA-Leu	Mitochondria	NA	NA	Maternally inherited	590050
COQ2	4q21.22	4-Hydroxybenzoate polyprenyltransferase, mitochondrial	Primary coenzyme Q_{10} deficiency type 1	AR	607426
ITGB4	17q25.1	Integrin β4	NA	AR	NA
LAMB2	3p21	Laminin subunit β2	Pierson syndrome	AR	609049
INF2	14q32	Inverted formin-2	Charcot–Marie–Tooth disease (dominant intermediate type E), FSGS type 5	AD	614455, 613237
MYH9	22q13.1	Myosin-9	Fechtner syndrome, Epstein syndrome	AR	153640, 153650
MYO1E	15q21	Unconventional myosin Ie	FSGS type 6	AR	614131
APOL1	22q13.1	Apolipoprotein L1	Nondiabetic causes of end-stage renal disease, FSGS	Sporadic	612551
COQ6	14q24	Ubiquinone biosynthesis mono-oxygenase COQ6	Primary coenzyme Q_{10} deficiency type 6	Sporadic	614647
PTPRO	12p12.3	Receptor-type tyrosine-protein phosphatase O	Nephrotic syndrome type 6	AR	614196

Abbreviations: AD, autosomal dominant; AR, autosomal recessive; FSGS, focal segmental glomerulosclerosis; OMIM, online Mendelian inheritance in man; NA, not available; SRNS, steroid-resistant nephrotic syndrome.

Jiang, S. *et al.* (Sept. 2013) The primary glomerulonephritides: a systems biology approach *Nat. Rev. Nephrol.* doi:10.1038/nrneph.2013.129

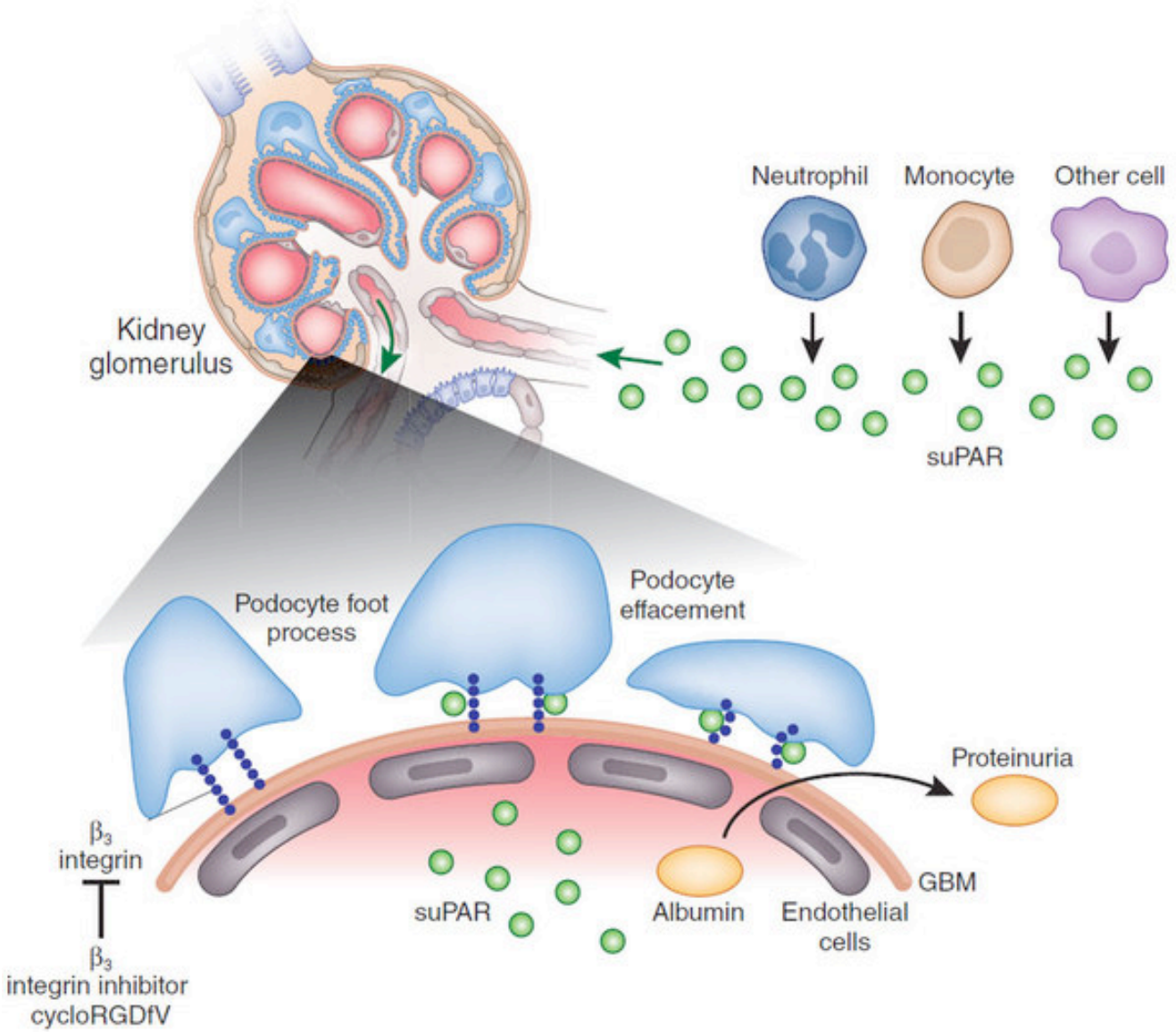
Glomerular endothelial cell surface layer, ESL, consists of the glycocalyx and the cell coat





Haraldsson, Nyström & Deen. Properties of the glomerular barrier and mechanisms of proteinuria. Physiol. Rev. 88: 451-487 2008;

suPAR and FSGS



Is suPAR (Soluble form of Urokinase Receptor) the circulating factor of FSGS?

Wei, C. *et al*. Nat. Med. 17, 952–960 (2011)

Research article

Inhibition of the TRPC5 ion channel protects the kidney filter

Thomas Schaldecker,[1] Sookyung Kim,[1] Constantine Tarabanis,[1] Dequan Tian,[1] Samy Hakroush,[1] Philip Castonguay,[1] Wooin Ahn,[1] Hanna Wallentin,[1] Hans Heid,[2] Corey R. Hopkins,[3] Craig W. Lindsley,[3] Antonio Riccio,[4] Lisa Buvall,[1] Astrid Weins,[1,5] and Anna Greka[1]

The Journal of Clinical Investigation http://www.jci.org Volume 123 Number 12 December 2013

nature medicine

Circulating angiopoietin-like 4 links proteinuria with hypertriglyceridemia in nephrotic syndrome

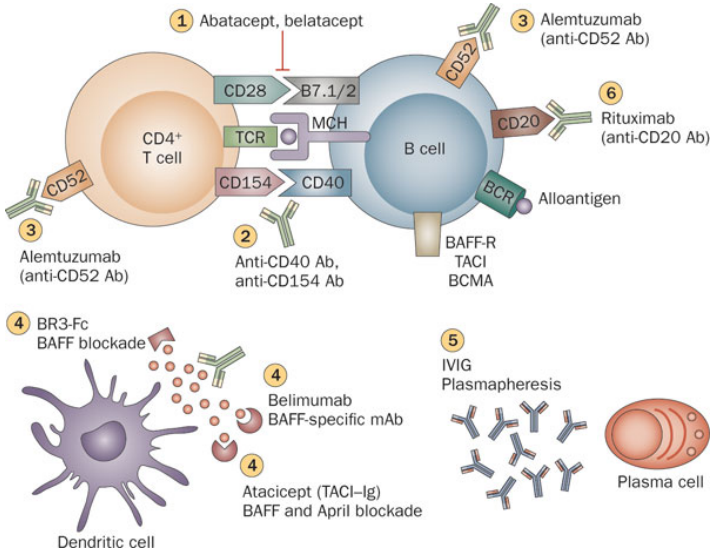
Lionel C Clement[1,6], Camille Macé[1,6], Carmen Avila-Casado[2,3], Jaap A Joles[4], Sander Kersten[5] & Sumant S Chugh[1]

The NEW ENGLAND JOURNAL of MEDICINE

BRIEF REPORT

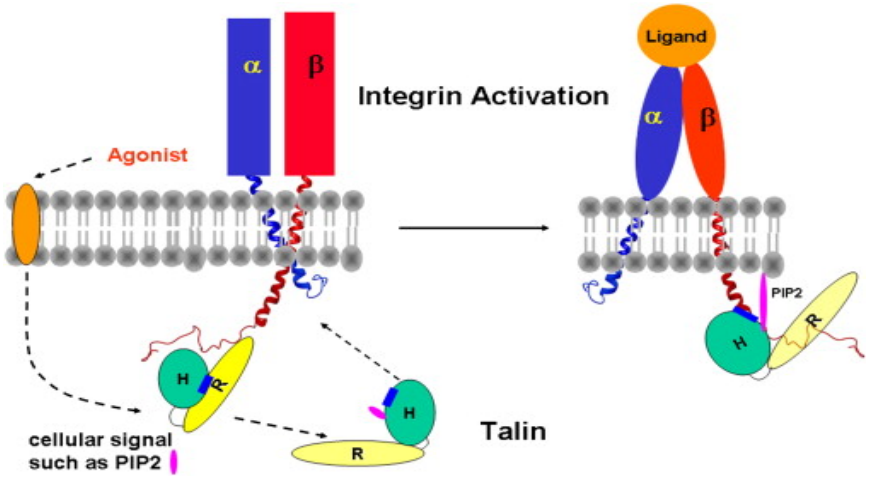
Abatacept in B7-1–Positive Proteinuric Kidney Disease

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.



A New Era of Podocyte-Targeted Therapy for Proteinuric Kidney Disease

Börje Haraldsson, M.D., Ph.D.

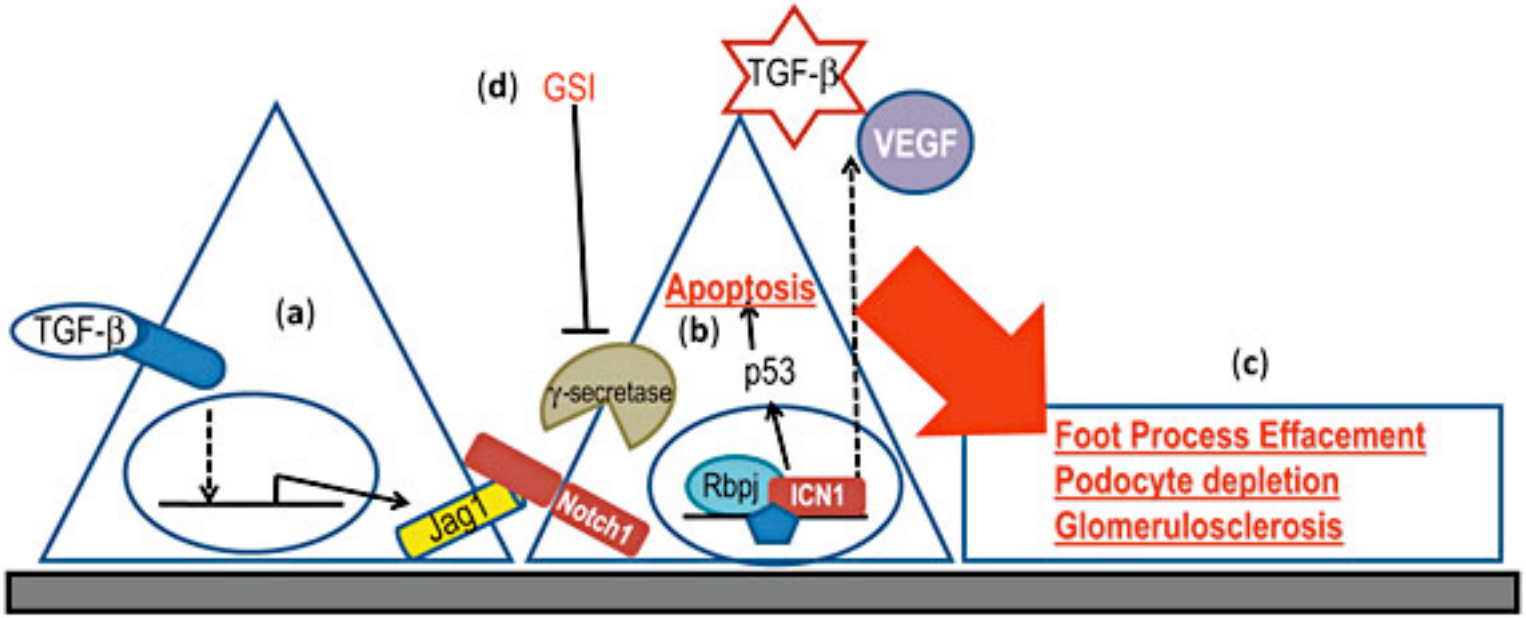


Role of Podocyte B7-1 in Diabetic Nephropathy

Paolo Fiorina,*† Andrea Vergani,*† Roberto Bassi,*†‡ Monika A. Niewczas,§ Mehmet M. Altintas,‖ Marcus G. Pezzolesi,§ Francesca D'Addio,*† Melissa Chin,* Sara Tezza,* Moufida Ben Nasr,* Deborah Mattinzoli,¶ Masami Ikehata,¶ Domenico Corradi,** Valerie Schumacher,* Lisa Buvall,†† Chih-Chuan Yu,‡‡§§ Jer-Ming Chang,§§ Stefano La Rosa,‖‖ Giovanna Finzi,‖‖ Anna Solini,¶¶ Flavio Vincenti,*** Maria Pia Rastaldi,¶ Jochen Reiser,‖ Andrzej S. Krolewski,§ Peter H. Mundel,†† and Mohamed H. Sayegh†††‡‡‡

J Am Soc Nephrol 25: ●●●–●●●, 2014. doi: 10.1681/ASN.2013050518

TGF-beta and FSGS



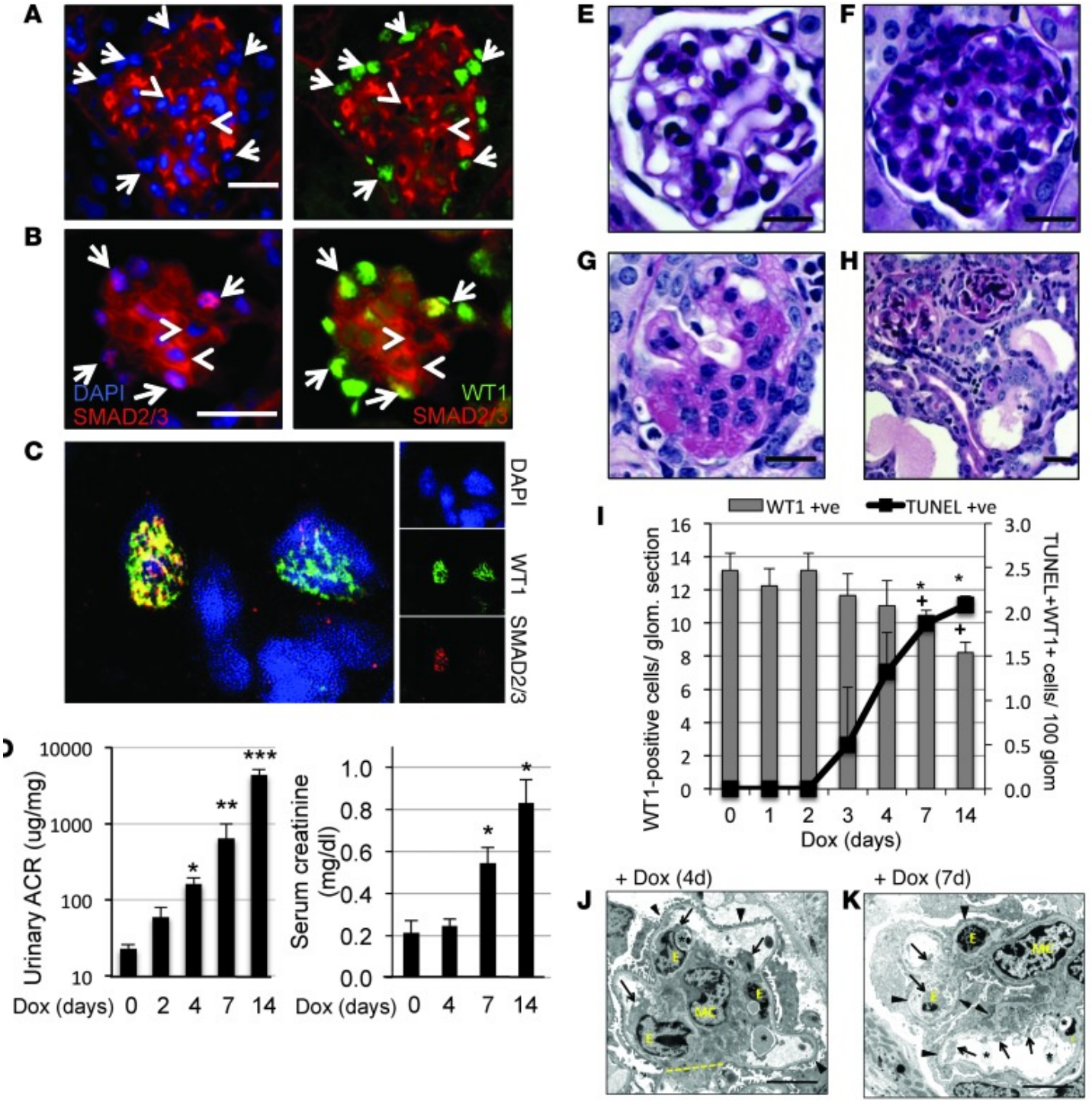
Endothelial mitochondrial oxidative stress determines podocyte depletion in segmental glomerulosclerosis

Ilse Daehn, Gabriella Casalena, Taoran Zhang, Shaolin Shi, Franz Fenninger, Nicholas Barasch, Liping Yu, Vivette D'Agati, Detlef Schlondorff, Wilhelm Kriz, Börje Haraldsson and Erwin P. Böttinger

J Clin Invest Apr 1, 2014, 124 (4):1608-1621

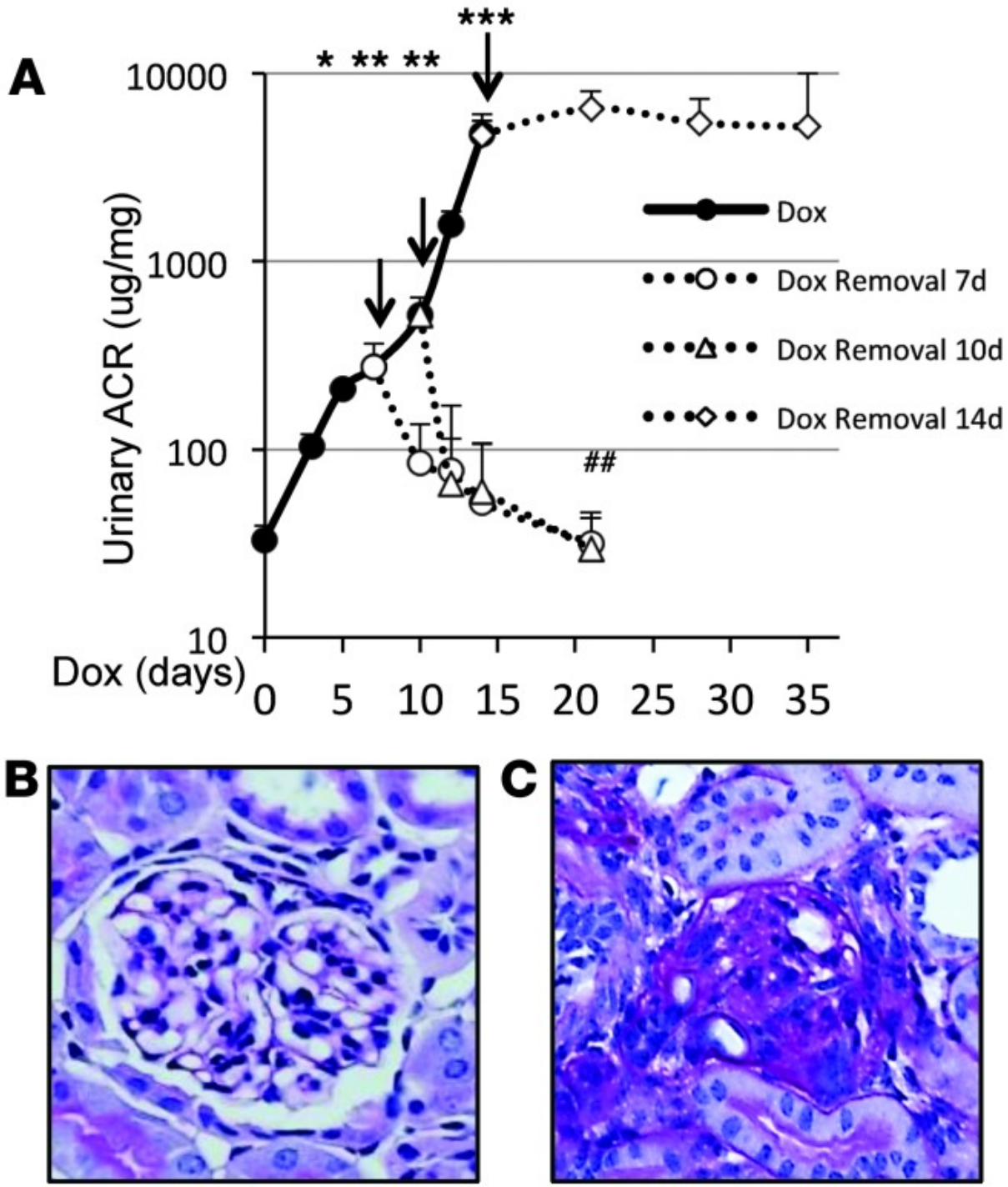
Experimental models

- Transgenic mouse – A conditional overexpression of constituently active TGF-beta 1 receptor in podocin-expressing cells (podocytes) – PodTbr1 mice
- Podocytes and endothelial cells in culture from the mice above (crossed with immortomouse)
- Adriamycin-induced FSGS
- Mice with podocyte-specific knockout of the micro-RNA processing enzyme dicer



Activation of podocyte-specific TGFβR1 induces podocytopathy with progressive glomerular disease and renal failure.

Daehn et al.
J Clin Invest
Apr 1, 2014, 124 (4): 1608-1621



TGFβR1 signaling in podocyte-induced albuminuria is reversible at days 7 and 10 but not day 14 of Dox treatment

Daehn et al.
J Clin Invest
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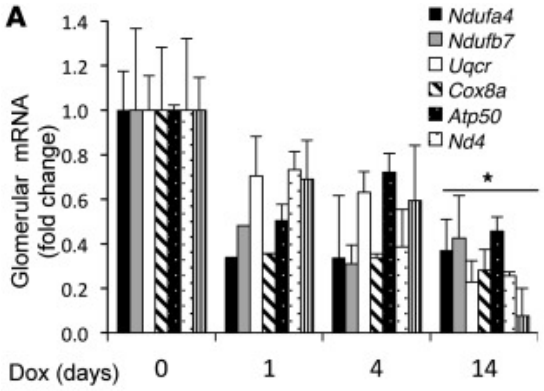
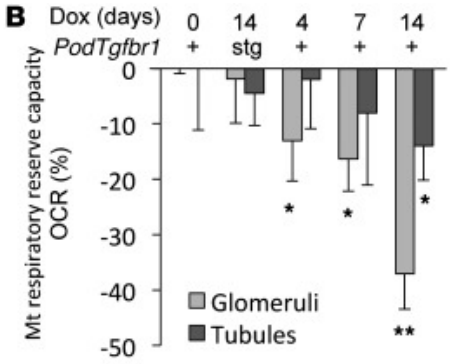
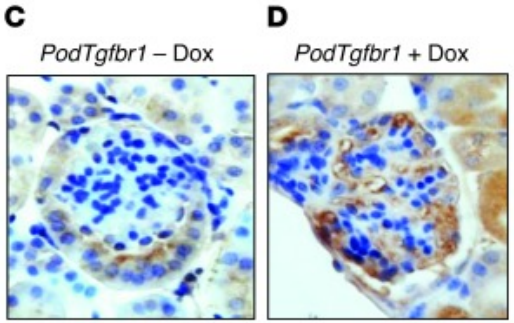
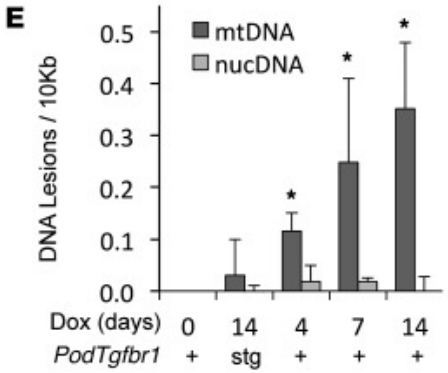
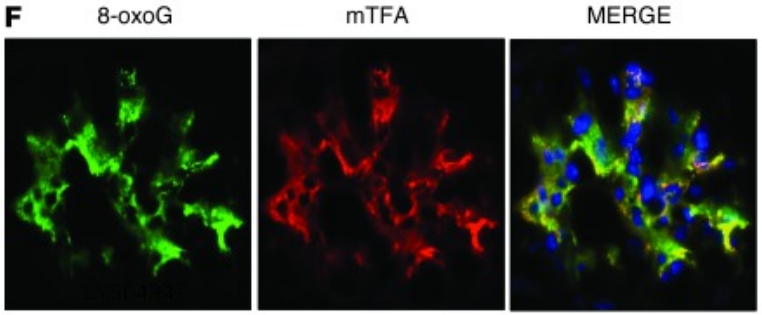
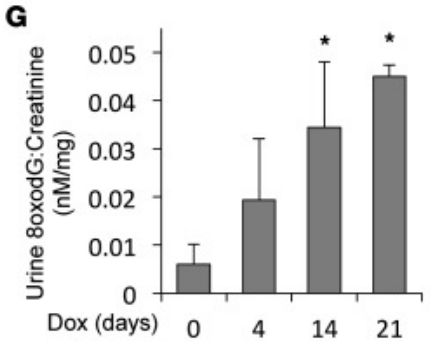


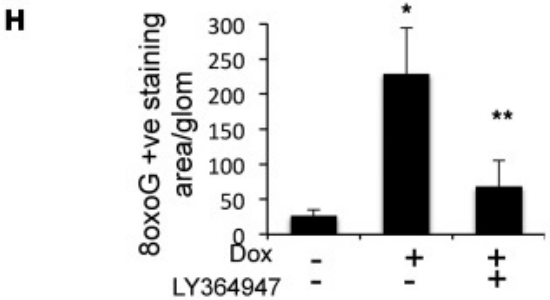






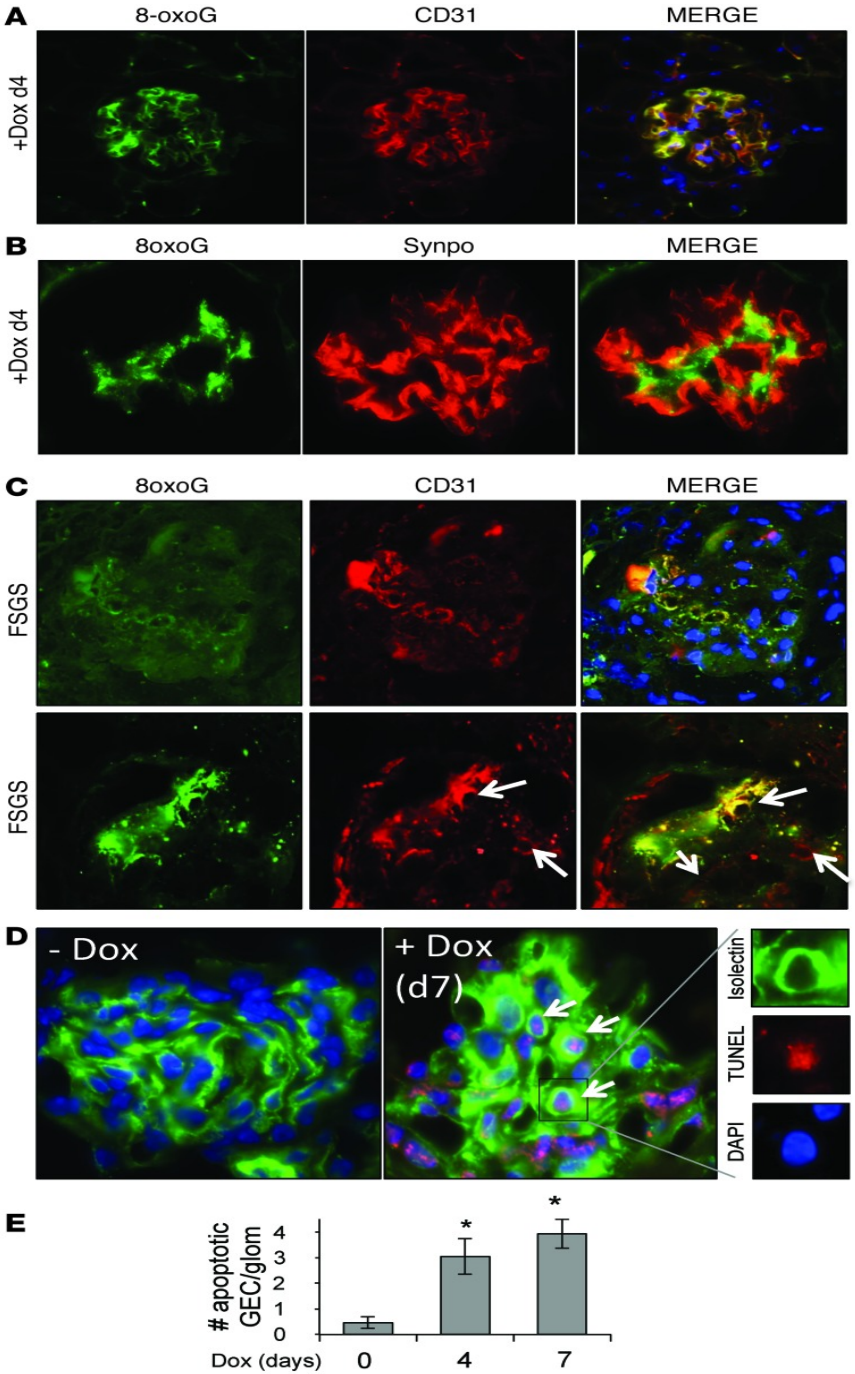






TGF-β signaling in podocytes decreased mitochondrial genes and function and increased mtDNA damage in glomerular cells

Daehn et al.
J Clin Invest
Apr 1, 2014, 124 (4): 1608-1621



TGF-β signaling in podocytes induces oxidative stress specifically in endothelial cells

Daehn et al.
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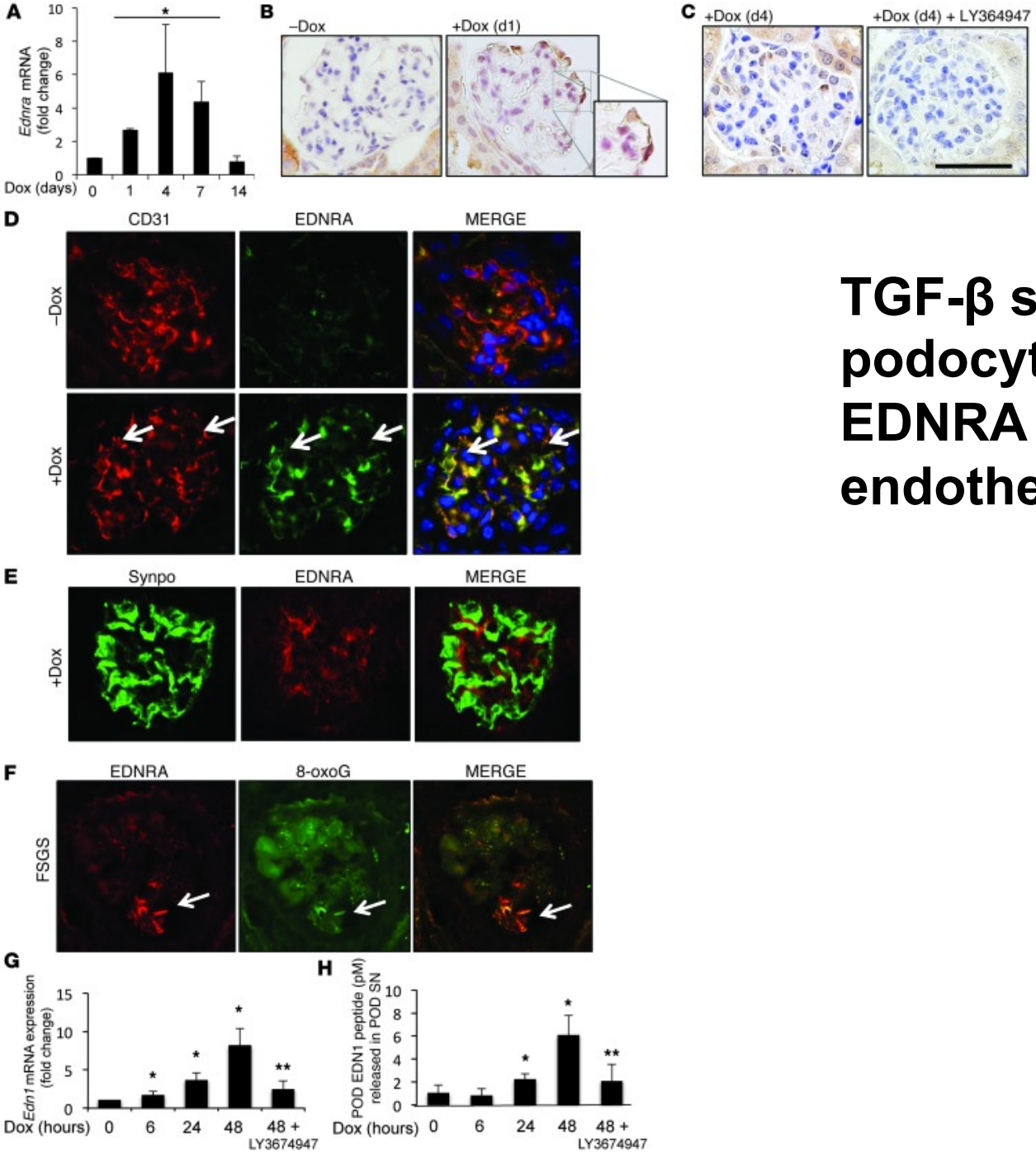
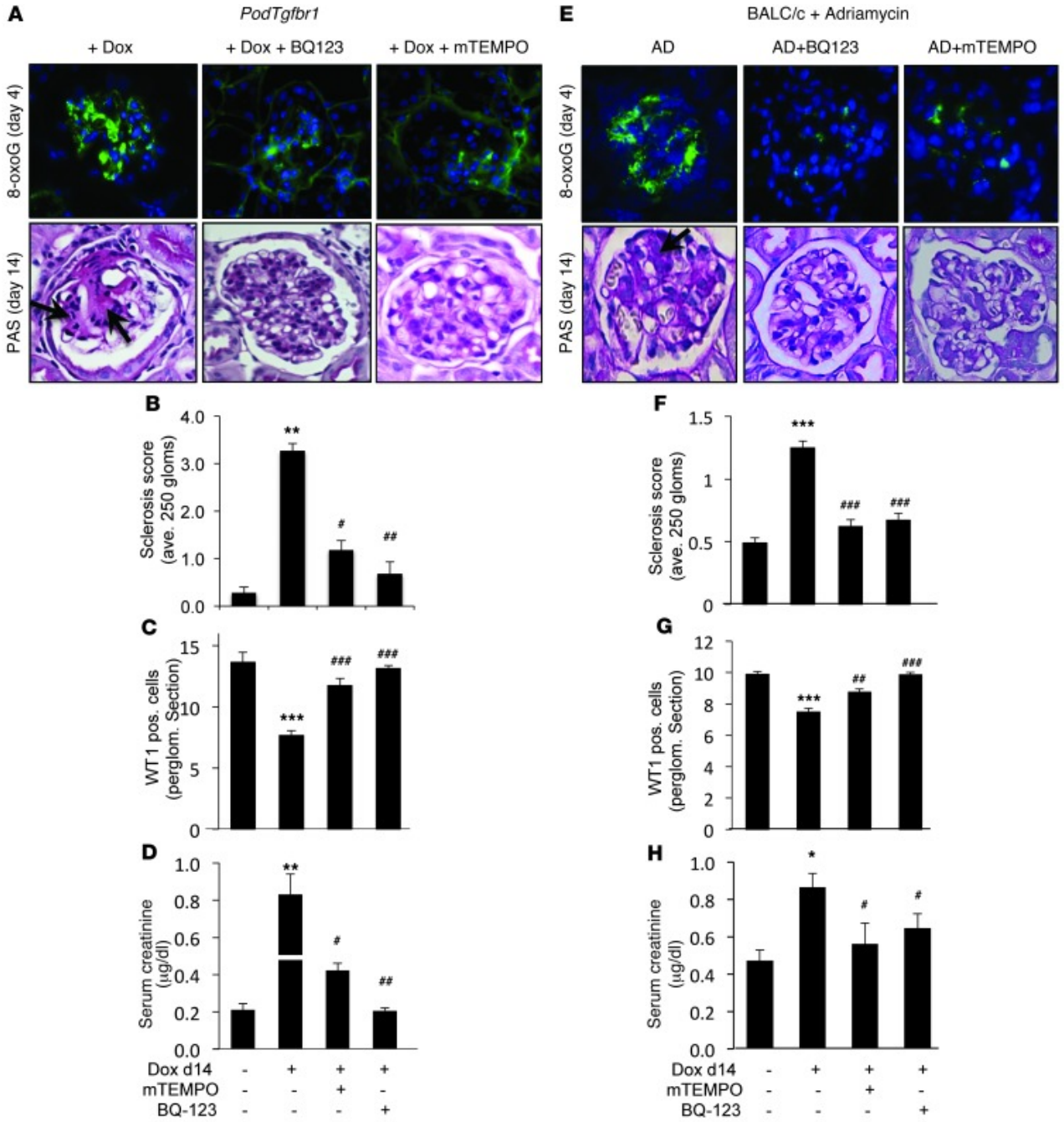


TGF-β signaling in podocytes induces EDNRA specifically in endothelial cells

Daehn et al.
J Clin Invest
Apr 1, 2014, 124 (4): 1608-1621



TGF-β signaling in podocytes induces specific EDN1-mediated mitochondrial oxidative stress specifically in endothelial cells

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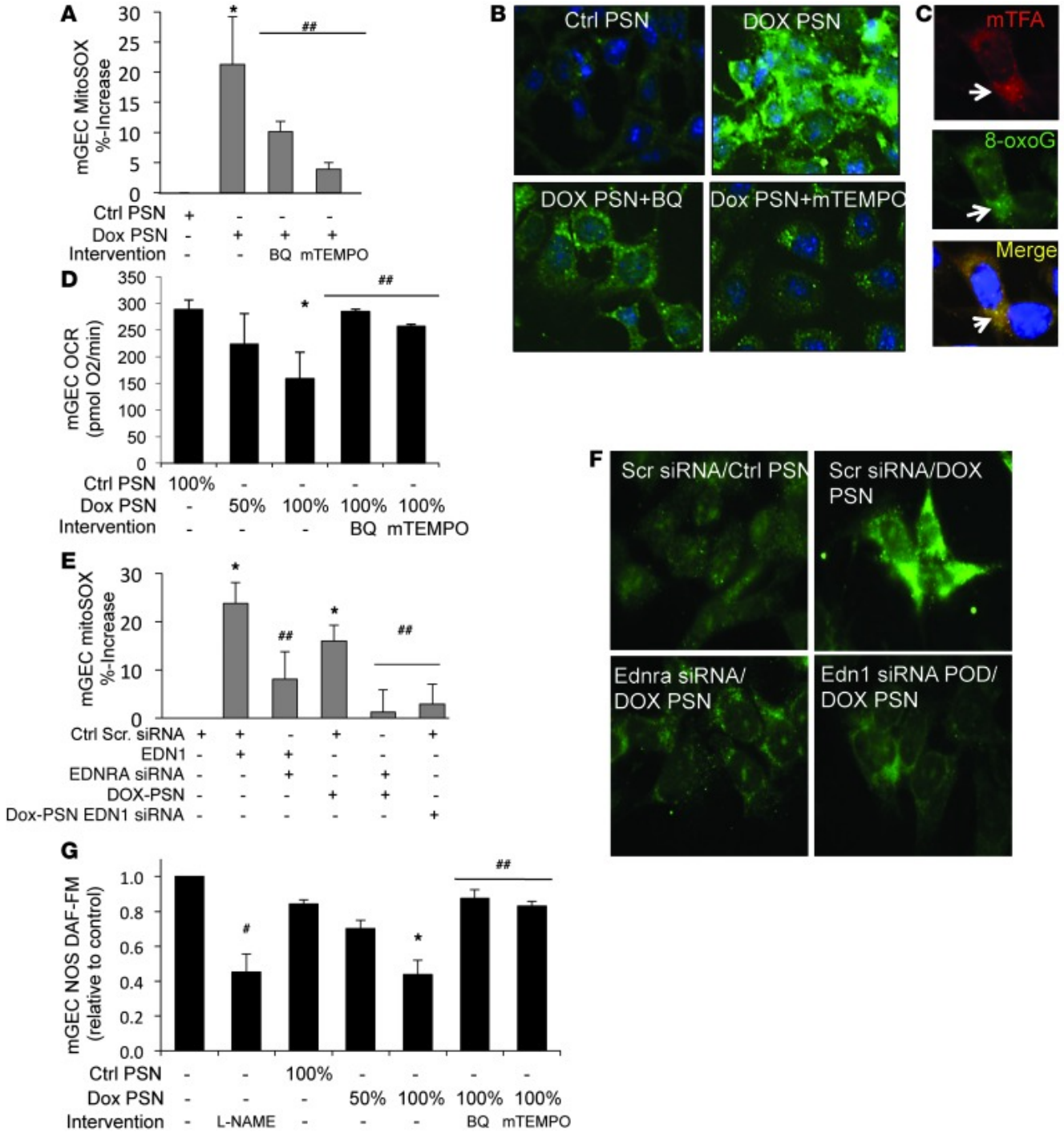
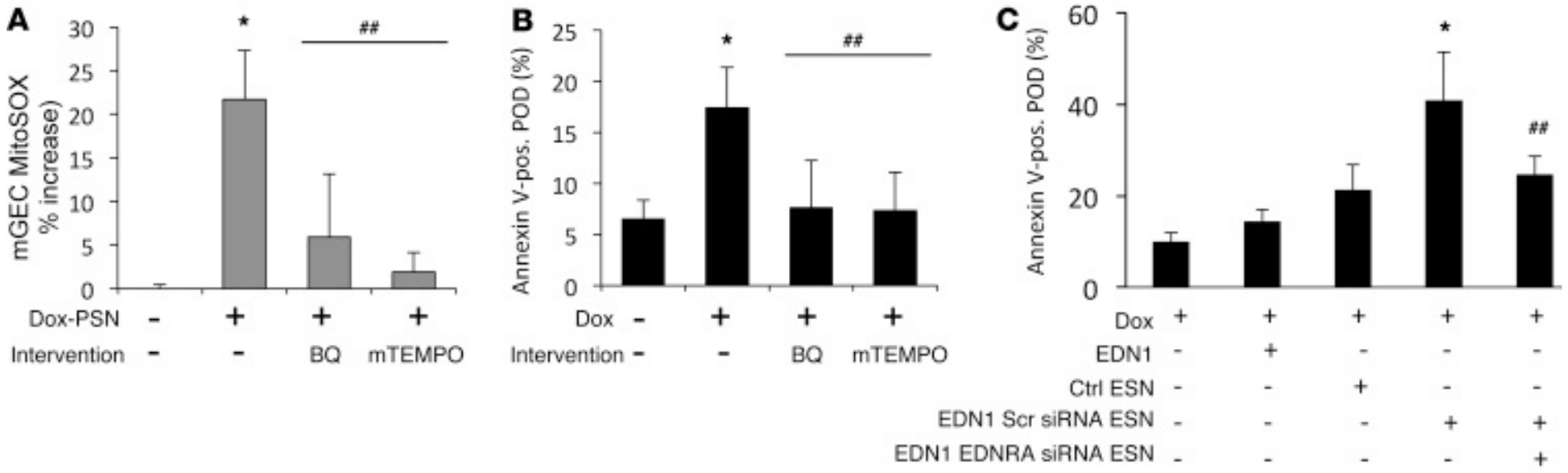


Validation of in vivo results using a defined *PodTgfbr1*-derived podocyte and in mGEC coculture system

Daehn et al.
J Clin Invest
Apr 1, 2014, 124 (4): 1608-1621

EDN1-mediated endothelial cell mitochondrial oxidative stress and dysfunction are required for podocyte apoptosis induced by TGF-β/SMAD signaling in cell death



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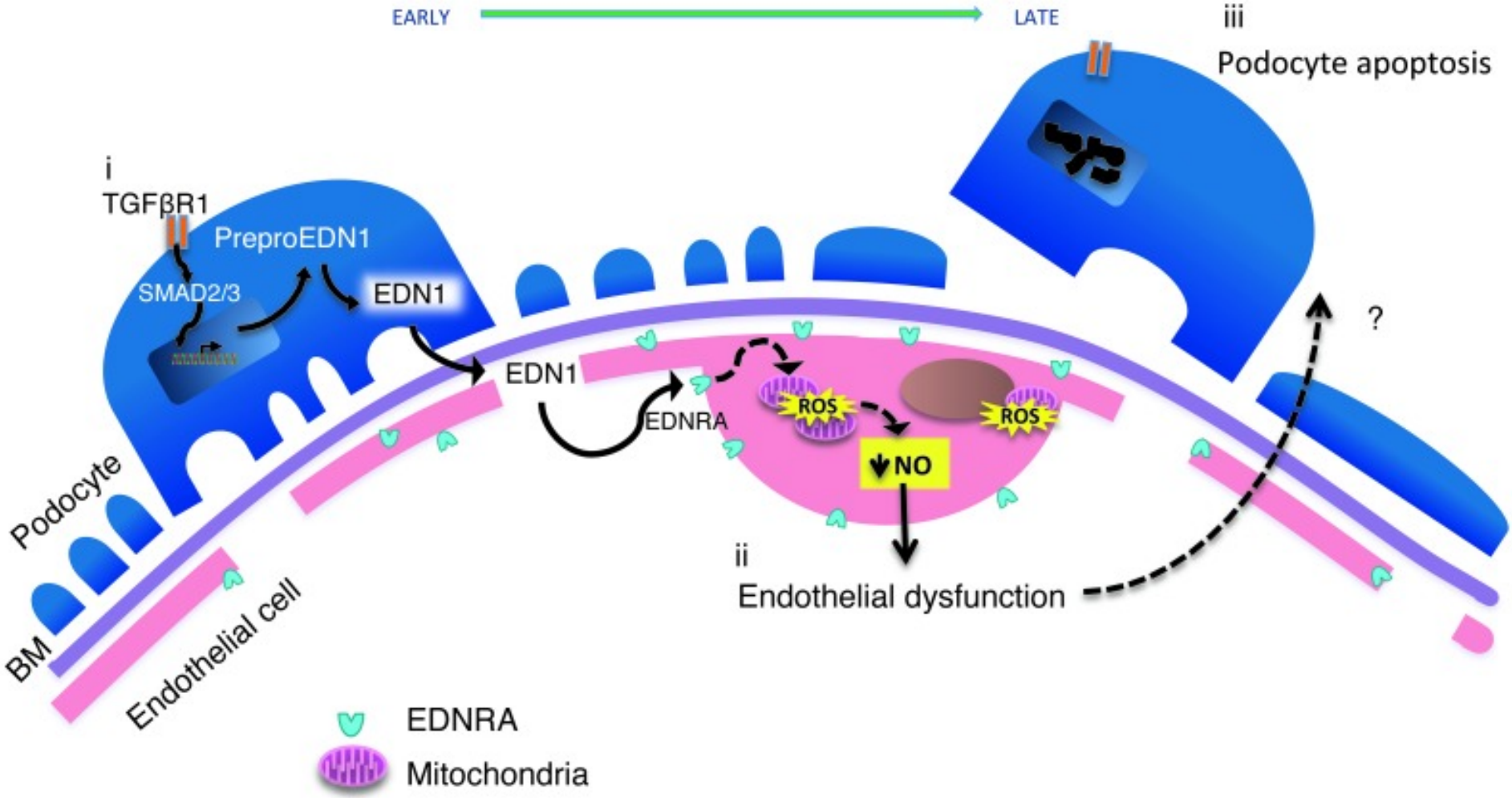
Working model of podocyte–glomerular endothelial cell crosstalk



Daehn et al. J Clin Invest
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The glomerular barrier in health and disease

- The glomerular barrier is highly size and charge selective
- Podocytes, endothelial and mesangial cells are all crucial components of the barrier
- The most important factor is the vivid and intricate communication between glomerular cells

Glomerular filtration is it like a water fall?

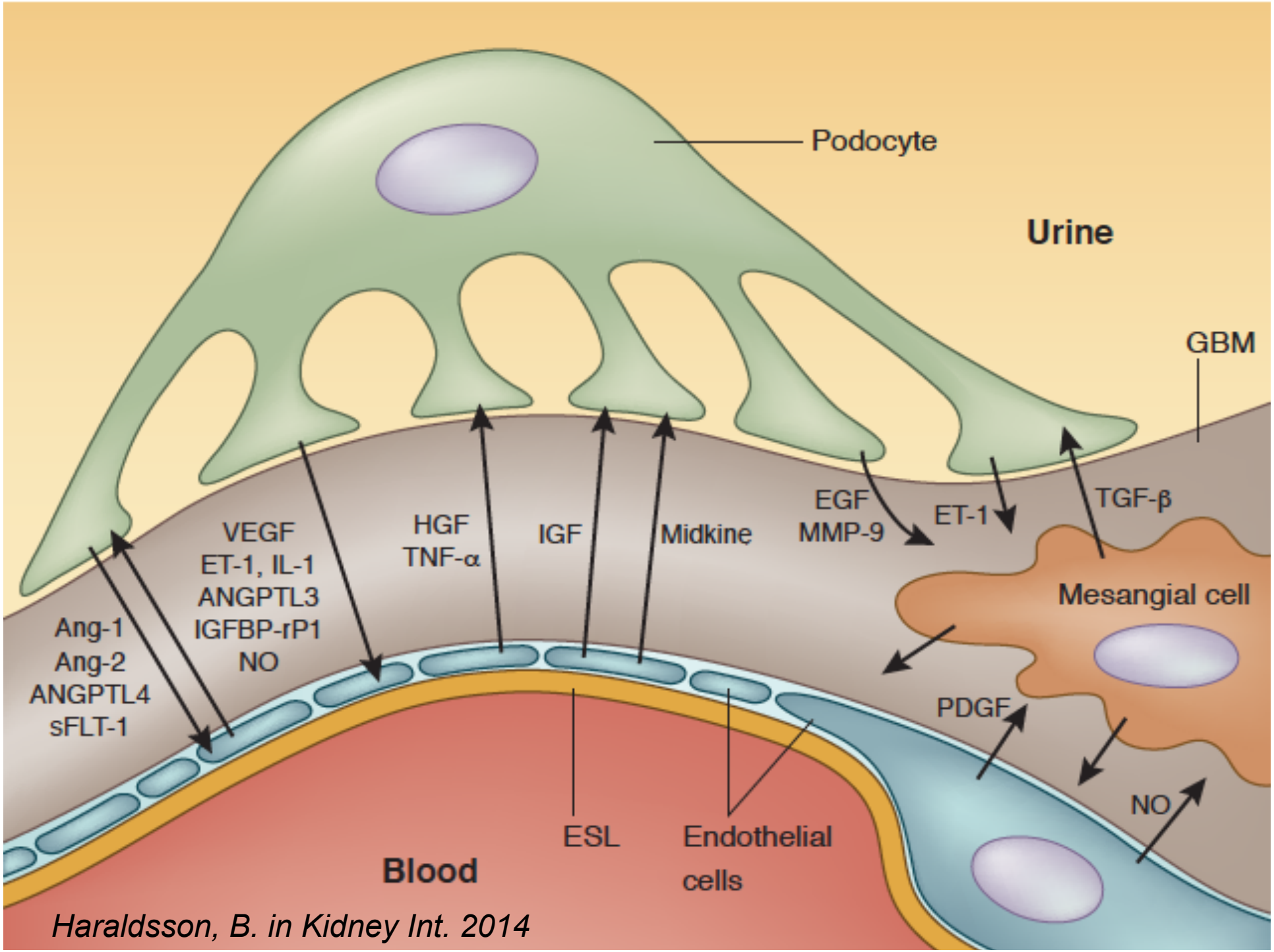
Nothing can move against the flow direction

Or is the glomerular filtration like a river?

It is really hard to move against the flow…

No, glomerular filtration looks like this!

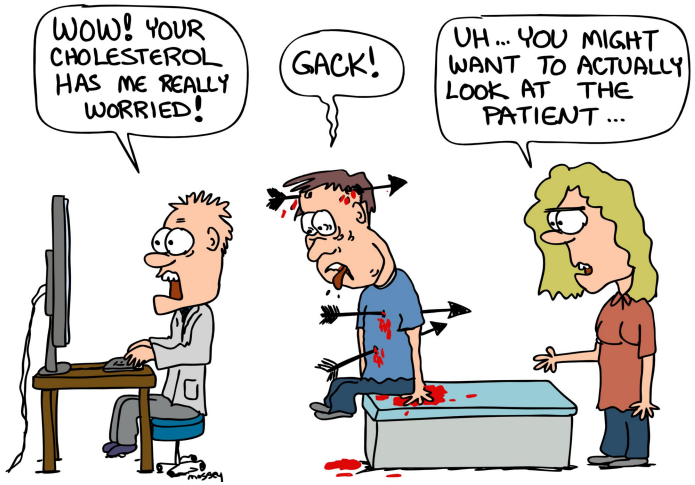
The Area is so huge that the flow velocity is extremely low



Haraldsson, B. in Kidney Int. 2014

"We have just started to learn a few notes of a glomerular cell symphony, of which we know little, and understand even less".

Thank you!



Questions?