Lipid Nephrotoxicity in diabetes: ‘Fatty Kidney’

Xiong Z. Ruan MD PhD

Renal-oriented Lipid Research Network

UCL Centre for Nephrology

SZU Centre for Nephrology

CQMU Centre for Lipid Research

Obesity epidemic is worldwide

Press release July 11, 2013

- UN Food and Agriculure Org(FAO) announces that adult obesity in Mexico(32.8%) has surpassed U.S.(31.8%)
  - 28% ages 5-9
  - 38% ages 10-19
- Egypt 34.6%
- Kuwait 42.8%
- Micronesia Nauru 71.1%
- China 22.8%

Impact of obesity on renal?

The parallel epidemics of obesity and chronic kidney disease

- A longitudinal cohort study of >8 million person-years of follow-up: BMI is an independent risk factor for ESRD after adjustment for traditional risk factors, including (but not limited to) age, sex, blood pressure, diabetes, and dyslipidemia.
  - BMI 25-30 kg/m^2 a relative risk of 1.9 for ESRD
  - BMI ≥ 40 kg/$m^{2:}$ 7.1 for ESRD

Ann Intern Med 2006;144(1):21-28
USRDS 2012 Annual Data Report
Am J Kidney Dis 2009;54(4):638-646.

- A BMI ≥ 25 kg/m^2 :an independent risk factor for progression of CKD in a follow-up of 162 cases of IgA nephropathy -

Am J Kidney Dis 2001;37(4):720-727

- Incidence of proteinuria and/or CKD in unilateral nephrectomy patients
  - BMI > 30 kg/$m^{2:}$ 92% developed proteinuria and/or CKD
  - BMI < 30 kg/m^2.12%

Kidney Int 2000;58(5):2111-2118.

脂质肾毒性假说 / 脂肪肾 （350 篇 SCI）

Glomerulo-atherosclerosis → CKD

LIPID NEPHROTOXICITY IN CHRONIC PROGRESSIVE GLOMERULAR AND TUBULO-INTERSTITIAL DISEASE

J. F. MOORHEAD M. K. CHAN
M. EL-NAHAS Z. VARGHESE

Department of Nephrology and Transplantation, Royal Free Hospital, London NW3 2QG

Moorhead & Varghese et al
Lancet 1982

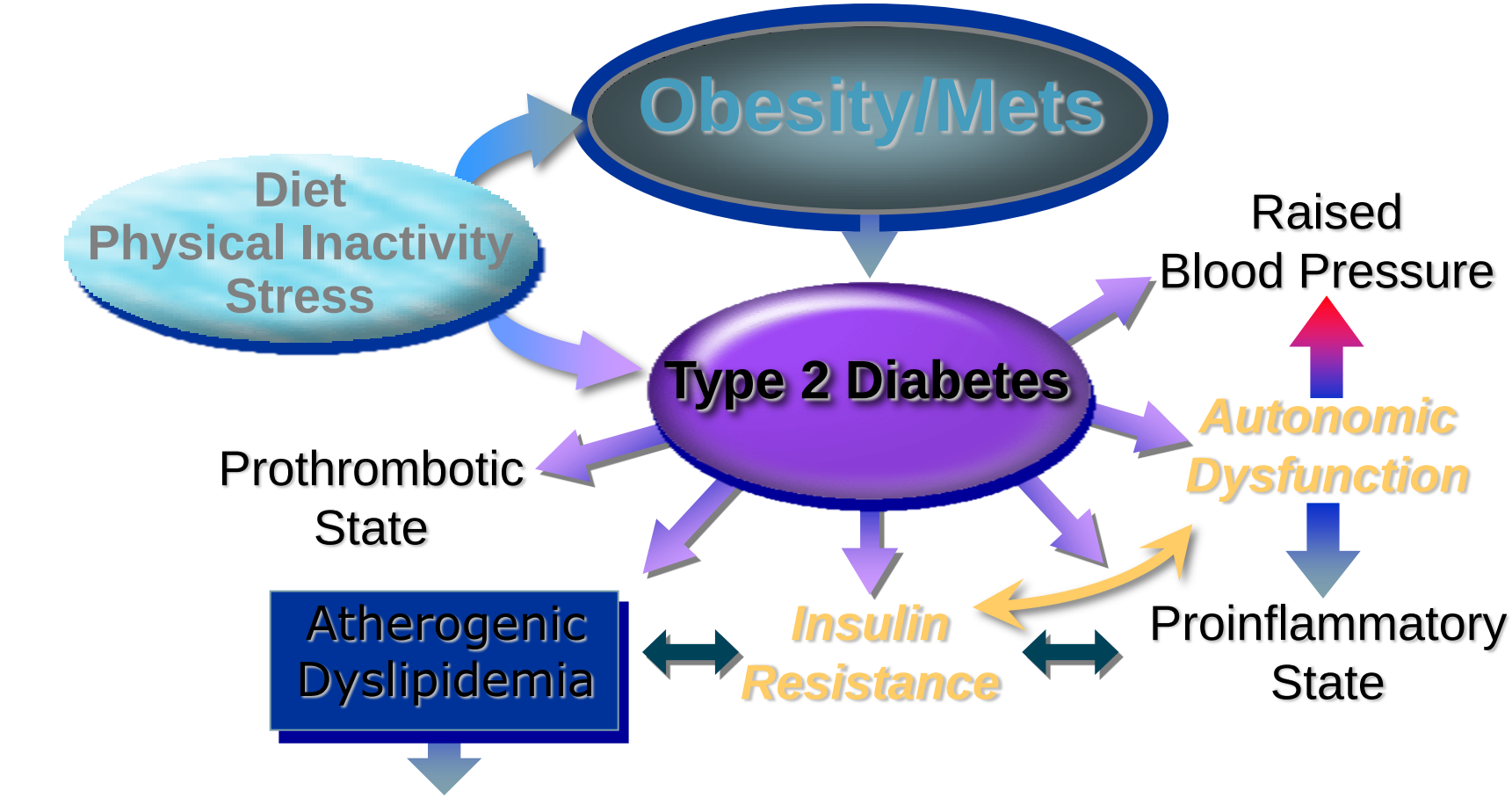
Aiko et al.
Lancet Diabetes and Endocrinology 2014

Obesity/DM

VLDL/FFA ↑ ↑
Small dense LDL ↑
LDL ↘
HDL ↓

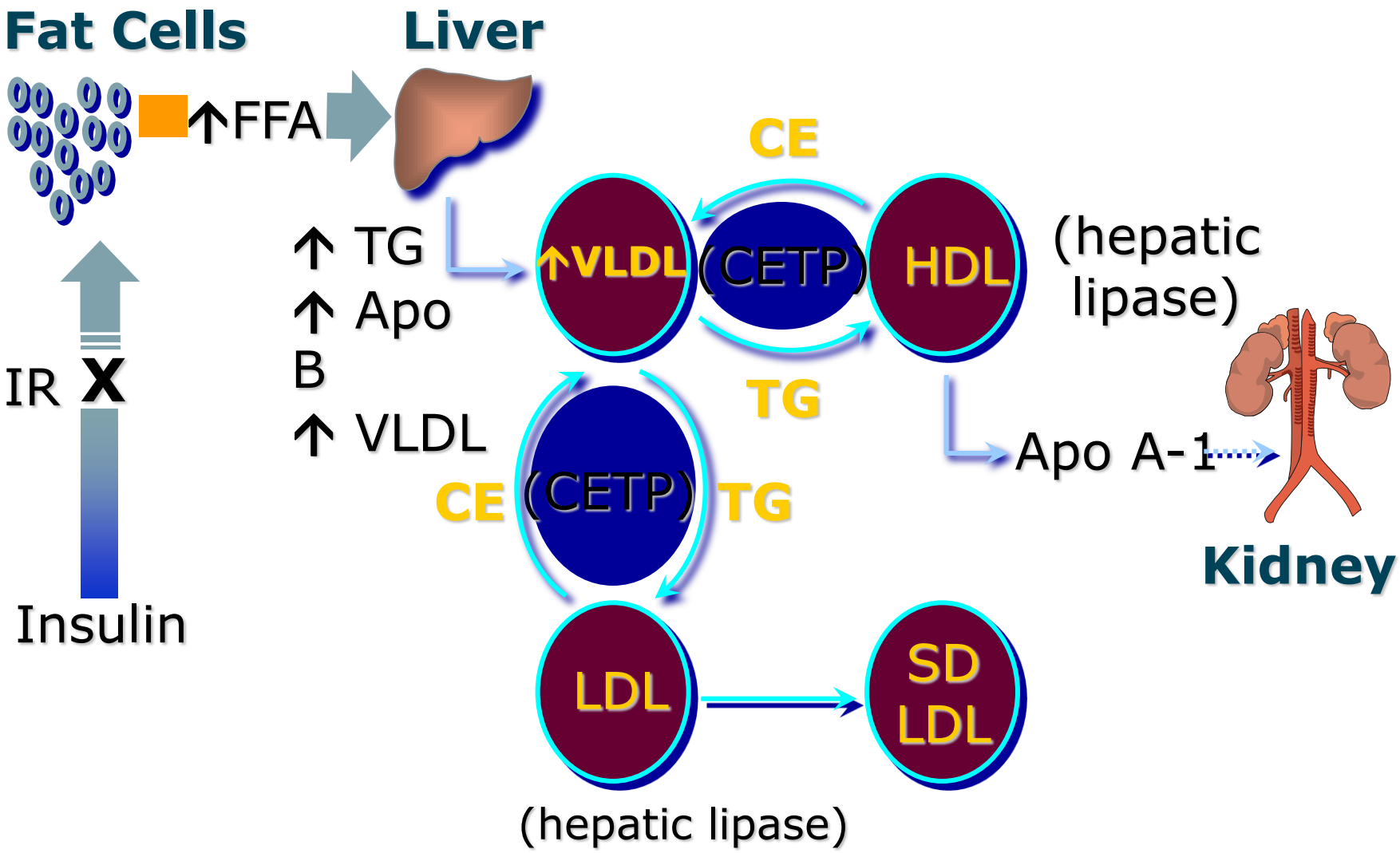
Ruan et al
Nature Rev Nephrol 2009

Obesity and Metabolic Syndrome: A Cluster of Coronary Heart Disease Risk Factors

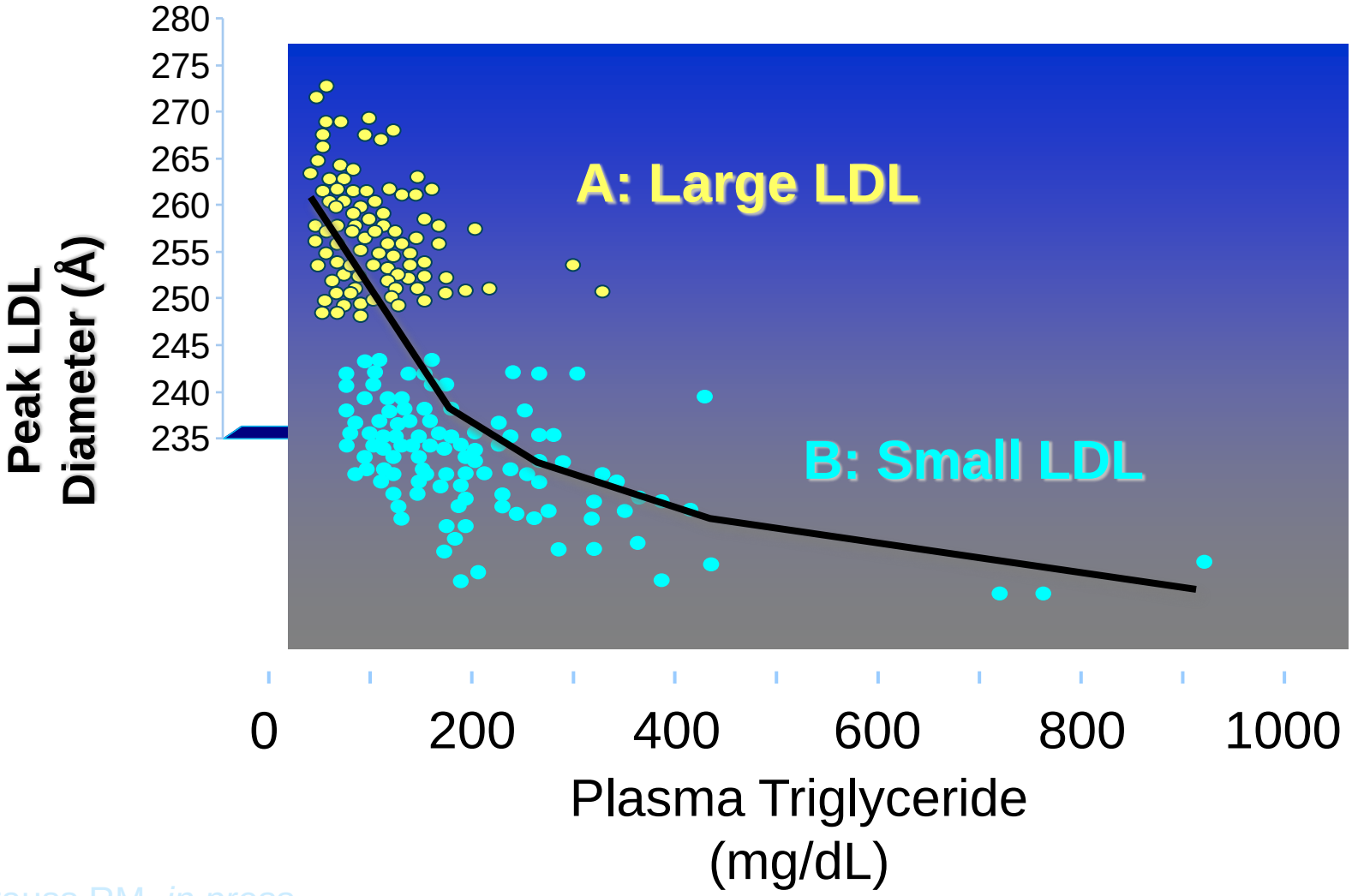


Adapted from Grundy SM. J Clin Endocrinol Metab. 2005;89:2595-2600.

Mechanisms Relating Insulin Resistance and Dyslipidemia

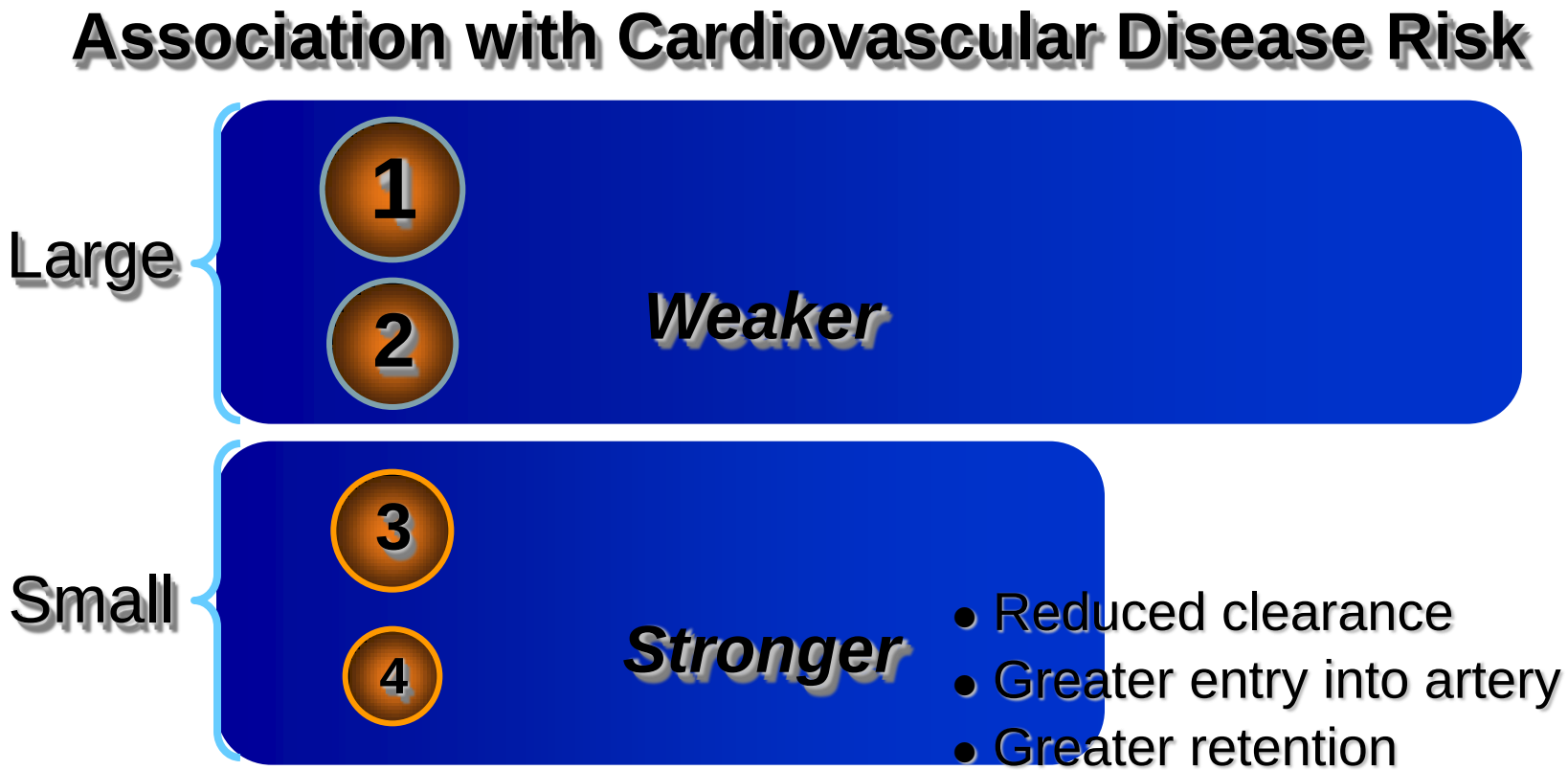


Relationship of Plasma Triglyceride to Peak Diameter of Low-Density Lipoprotein (LDL)



Krauss RM, *in press*

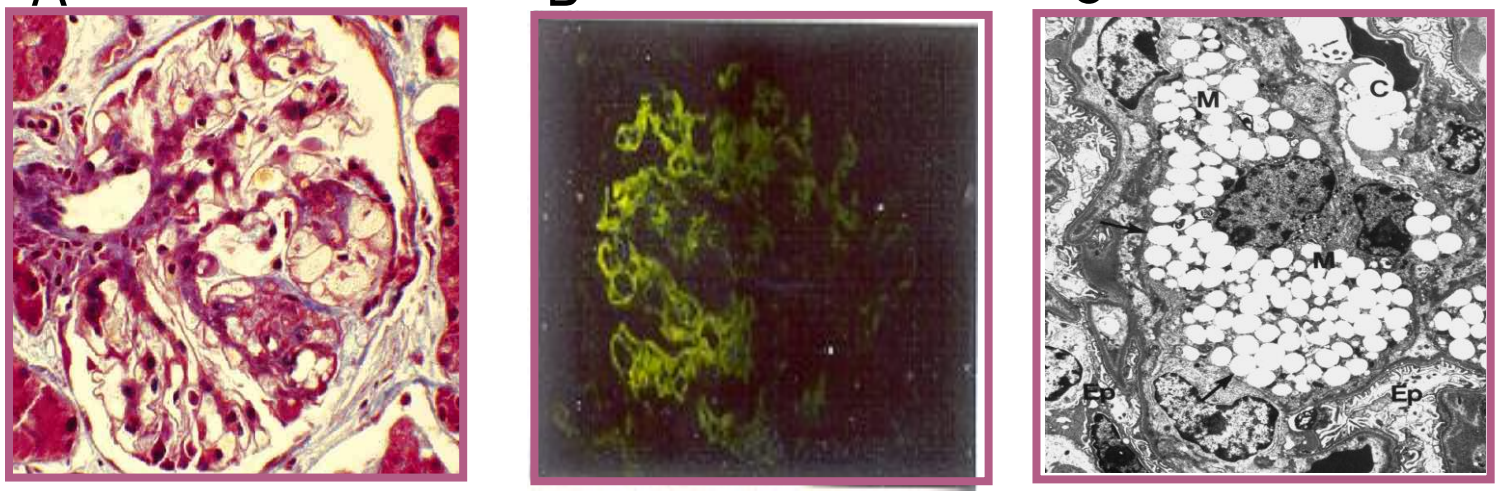
Low-Density Lipoprotein (LDL) Consists of Multiple Distinct Subclasses Differing in Size and Lipid Content*



* Distribution of subclasses is independent of LDL-cholesterol.

Berneis KK, Krauss RM. *J Lipid Res.* 2002;43:1363-1379.

Lipid nephrotoxicity: promise



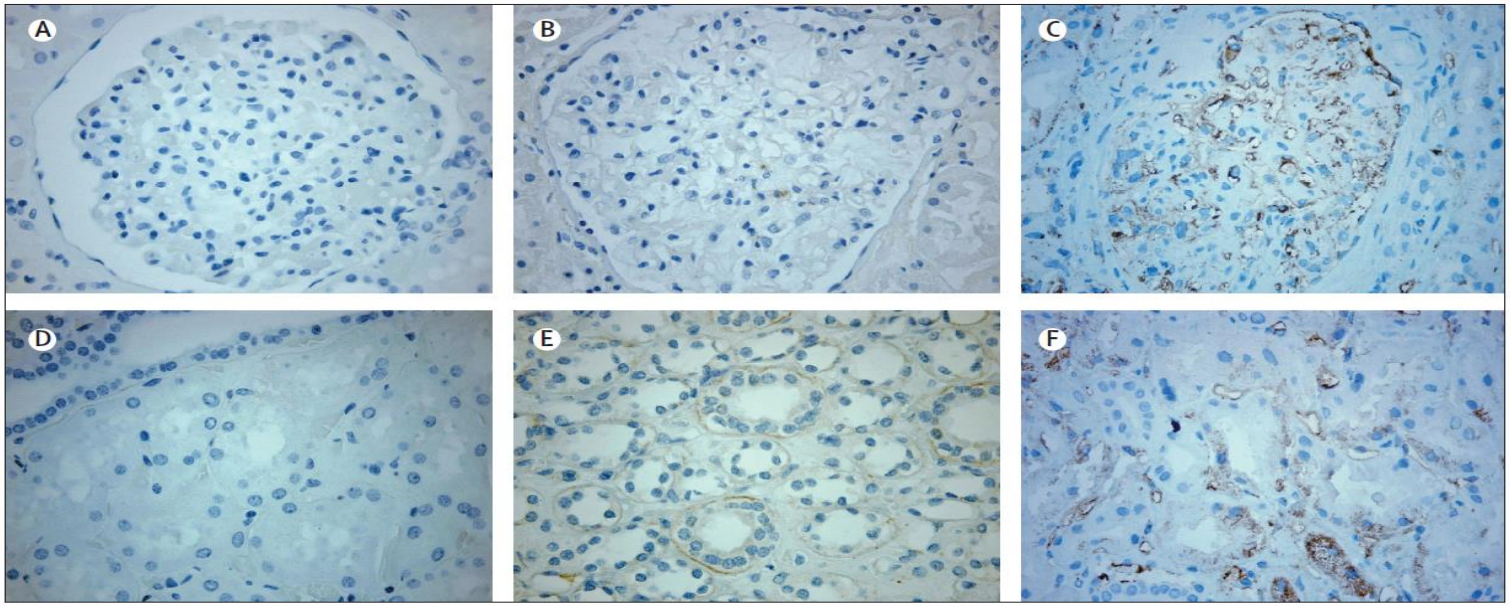
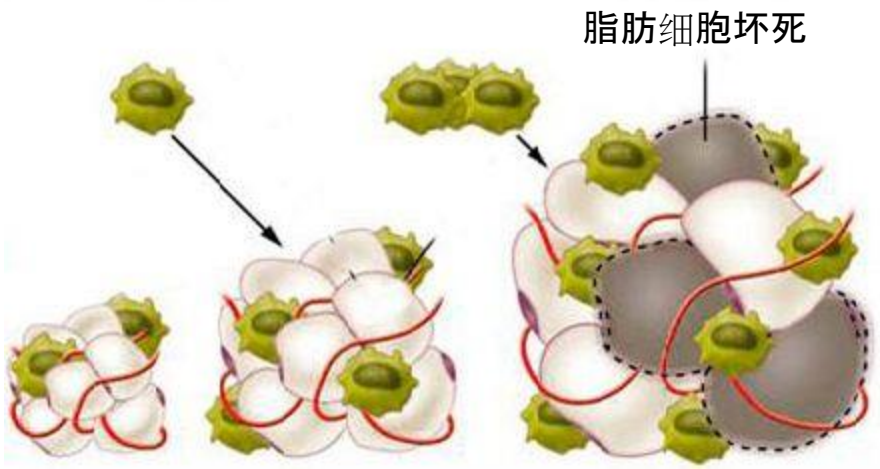


Figure 2: Adipophilin staining showing lipid droplets in kidney tissue of three patients
(A, D) Metabolically healthy obese patients (without metabolic syndrome); no lipid deposits are observed. (B, E) Metabolically unhealthy obese patient (with metabolic syndrome); lipid droplets observed in the glomeruli (B) and in the basal site of the tubular epithelial cells (E). (C, F) Type 2 diabetic nephropathy; massive deposits seen in the glomeruli (C) in visceral and parietal epithelial cells, and in the basal and apical site of the tubular cells (F). Magnification ×400.

代谢性炎症(Metaflammation):

由摄入营养物质和代谢过剩触发的一种慢性低丰度炎症



炎症因子:
TNF-α, IL-6 ,
IL-1β, SAA,
MCP-1等

脂肪因子:
↑resistin,
↓adiponectin

脂肪、肝脏、肌肉等胰岛素敏感组织发生胰岛素抵抗

Hotamisligil G S. Nature, 2006, 444(7121):860 867.

脂质肾毒性假说 / 脂肪肾 （350 篇 SCI）

Glomerulo-atherosclerosis

CKD

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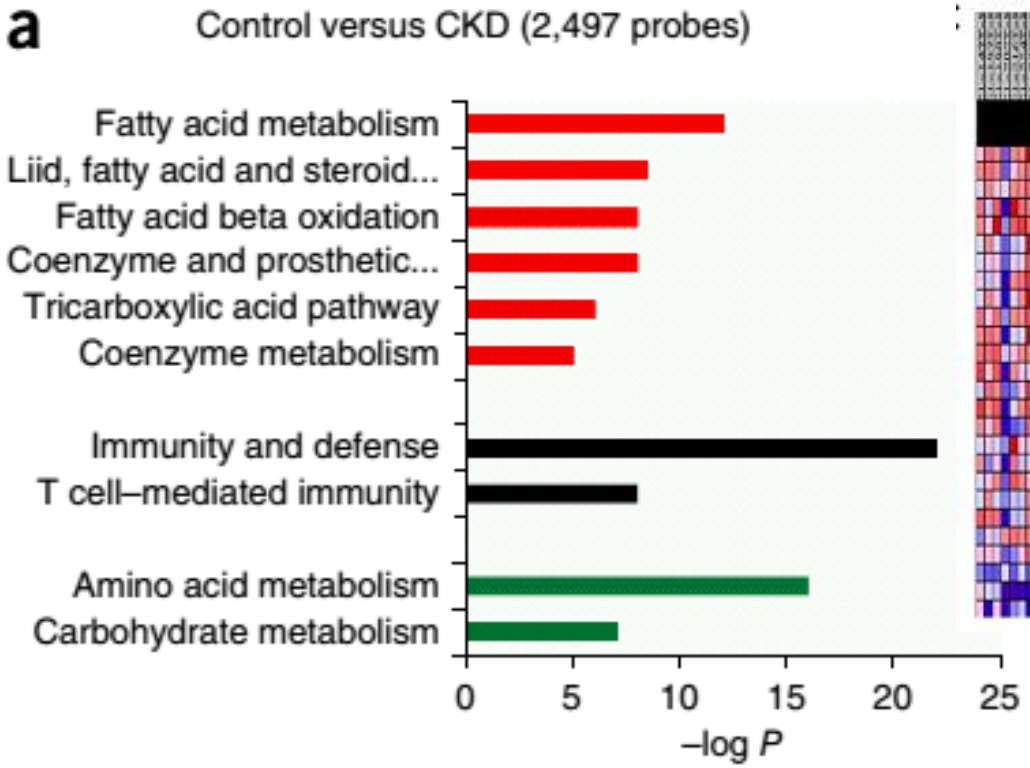
Nature Rev Nephrol 2009

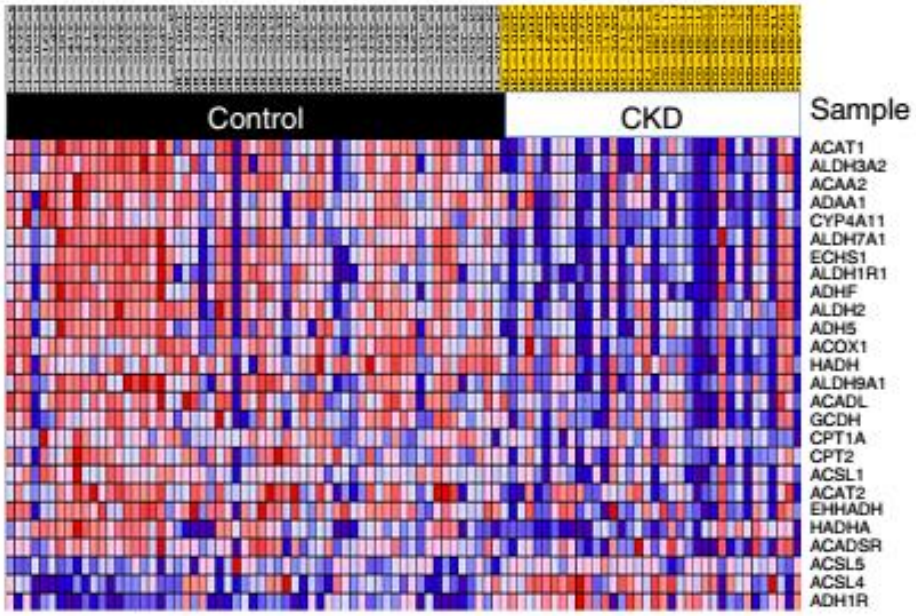
Ma, et al **Hepatology 2009**

Inflammation

Lipid nephrotoxicity: promise

genome-wide transcript-level

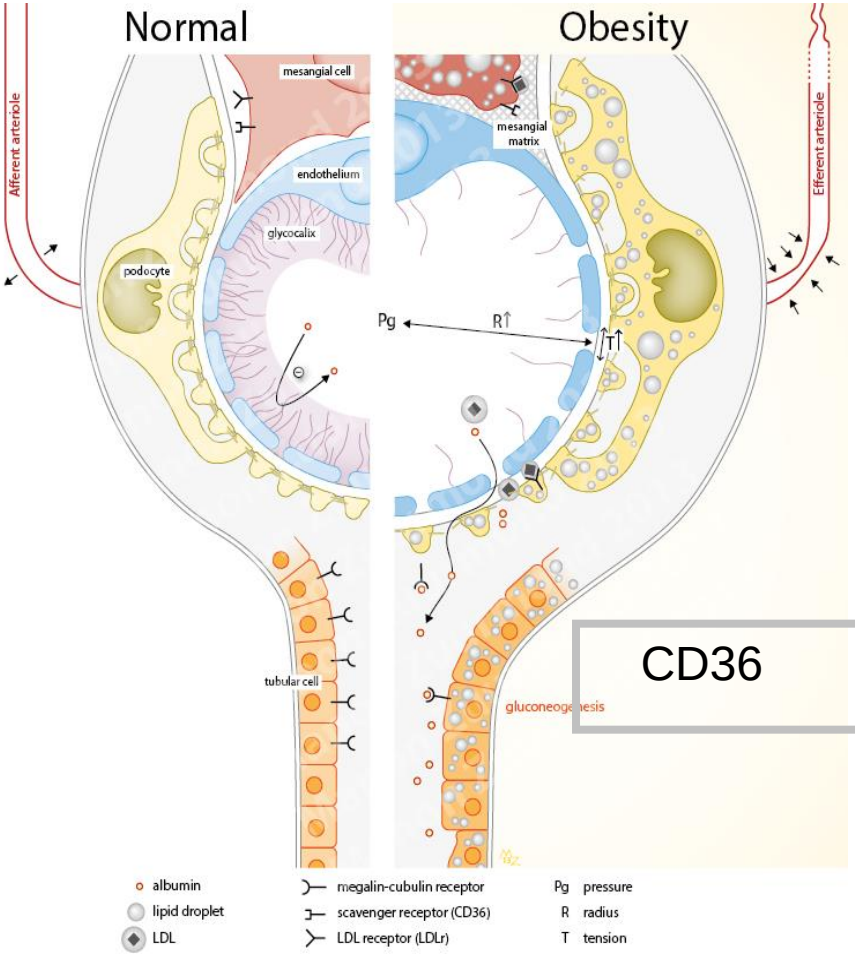




2,497 transcripts，(n= 95) microdissected human kidney samples，diabetes- and hypertension-induced TIF are almost indistinguishable.

Kang HM, Nature Medicine 2014

Lipid nephrotoxicity: mechanisms?



Review

Fatty kidney: emerging role of ectopic lipid in obesity-related renal disease

Aiko P J de Vries, Piero Ruggenenti, Xiong Z Ruan, Manuel Praga, Josep M Cruzado, Ingeborg M Bajema, Vivette D D'Agati, Hildo J Lamb, Drazenka Pongrac Barlovic, Radovan Hojs, Manuela Abbate, Rosa Rodriquez, Carl Erik Mogensen, Esteban Porrini, for the ERA-EDTA Working Group Diabesity

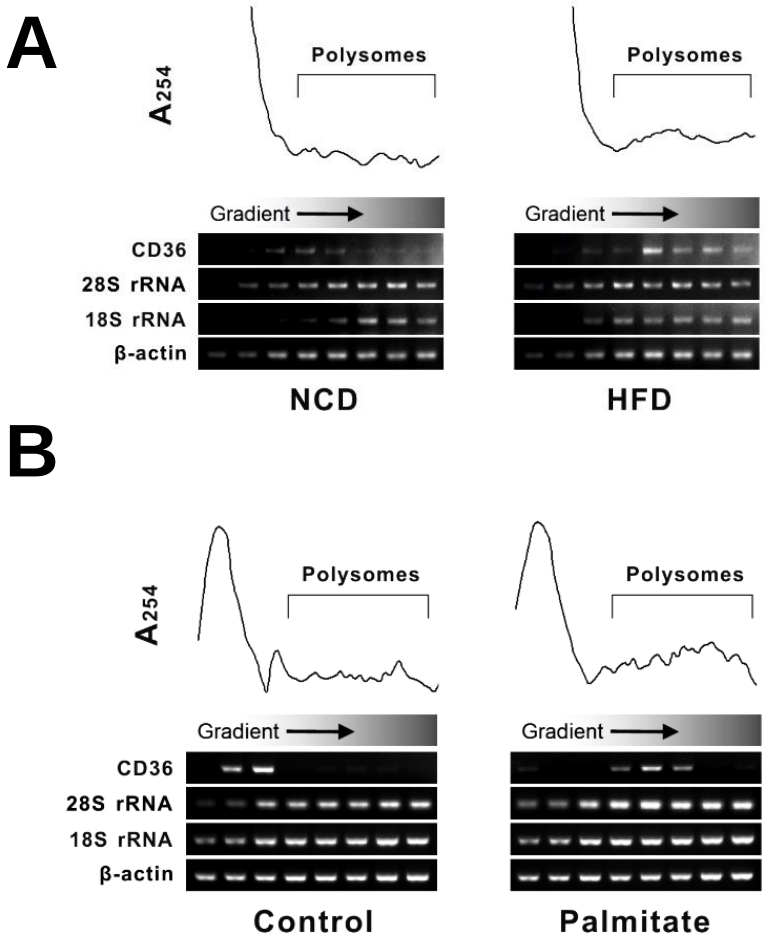
The global increase in chronic kidney disease (CKD) parallels the obesity epidemic. Obesity conveys a gradual but independent risk of progression of CKD that seems irrespective of the underlying nephropathy. Obesity has been associated with a secondary focal segmental glomerulosclerosis coined obesity-related glomerulopathy (ORG). Pathways through which obesity might cause renal disease are not well understood, and early clinical biomarkers for incipient ORG or renal relevant obesity are currently lacking. Recent human and experimental studies have associated ectopic lipid accumulation in the kidney (fatty kidney) with obesity-related renal disease. There is enough growing insight that ectopic lipid—the accumulation of lipid in non-adipose tissue—is associated with structural and functional changes of mesangial cells, podocytes, and proximal tubular cells to propose the development of ORG as a maladaptive response to hyperfiltration and albuminuria. Recent advances in metabolic imaging might validate ectopic lipid as a biomarker and research aid, to help translate novel therapeutics from experimental models to patients.

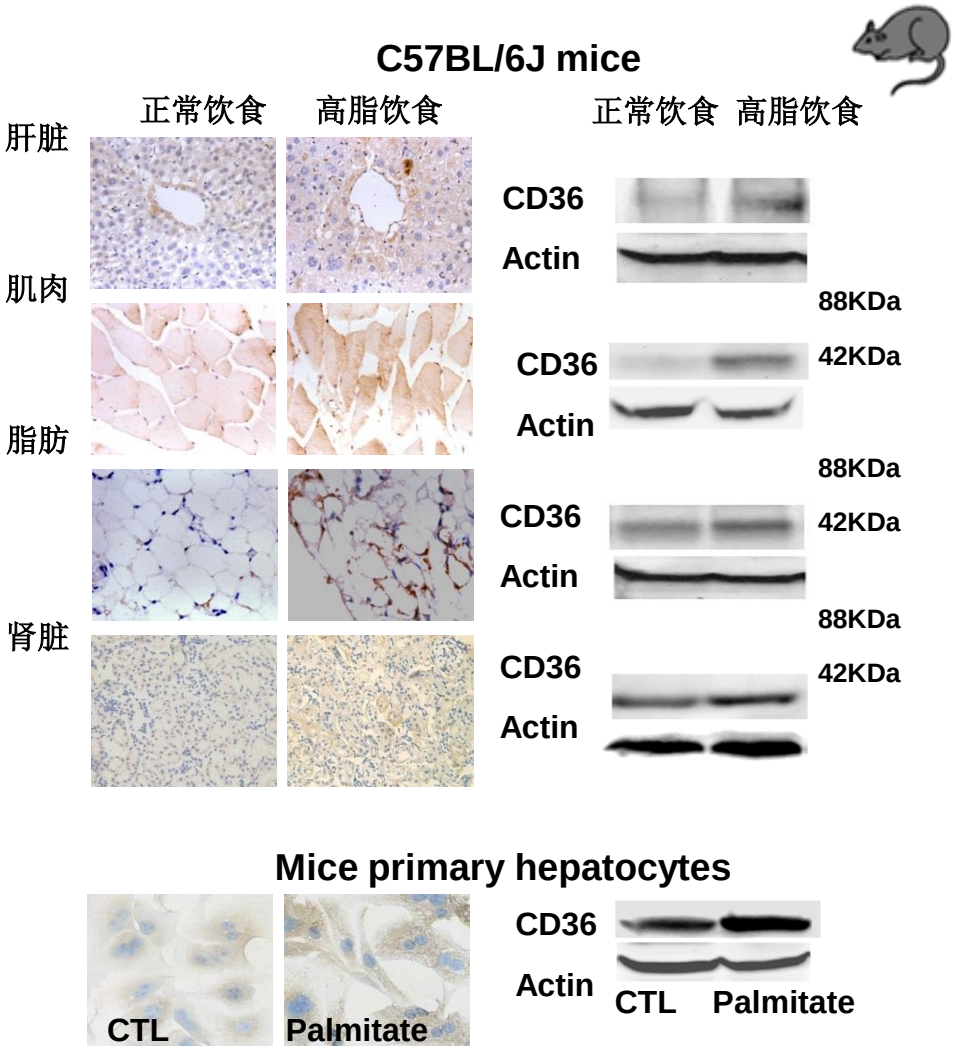
Lancet Diabetes Endocrinol 2014; 2: 417–26

Department of Nephrology (A P J de Vries MD), Department of Pathology (I M Bajema MD), and Department of Radiology (H J Lamb MD), Leiden University Medical Center and Leiden University, Leiden, Netherlands; IRCCS—Istituto di Ricerche Farmacologiche Mario Negri, Clinical Research Center for Rare Diseases "Aldo e Cele Dacco".

Fatty acid transporter CD36 and renal injury

Effect of palmitate /HFD on CD36 translational efficiency and protein expression





Unpublished data

Fatty acid transporter CD36 and renal injury

Inducible expression of CD36 in kidney

Figure 3. Inflammation and Palmitic acid (PA)causes CD36 translocation from cytoplasm to the ER , accompanying a ER stress in HK2 cells

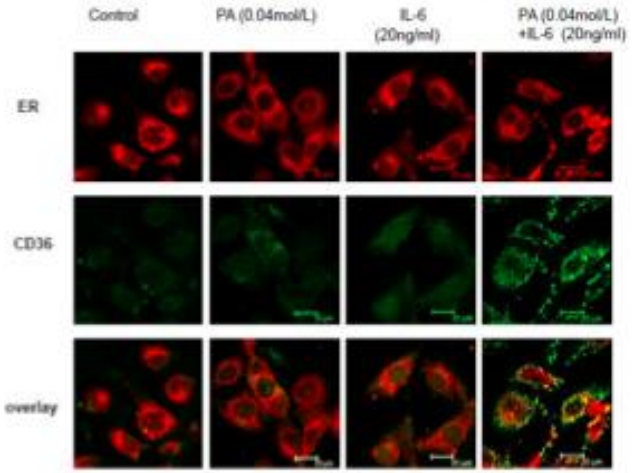
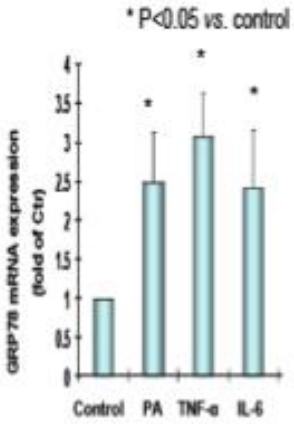


Figure 4. Inflammatory stress induced endoplasmic reticulum stress



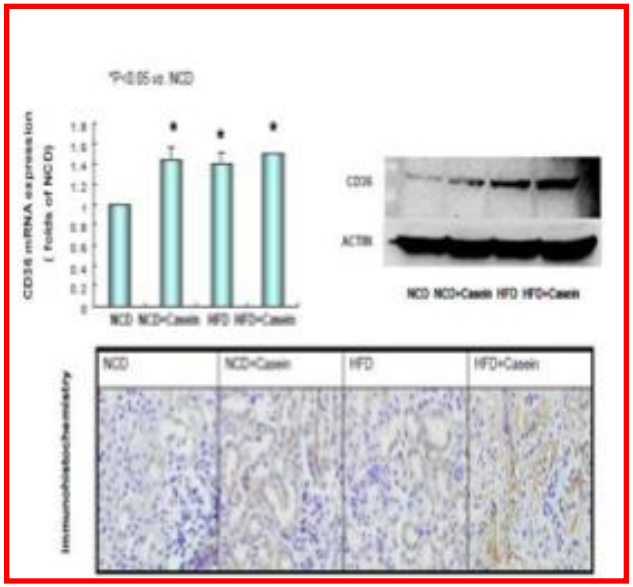


Figure 6. MIS induced by Casein injection and hyperlipidaemia enhances lipid accumulation which could be reduced by genetic deletion of scavenger receptors

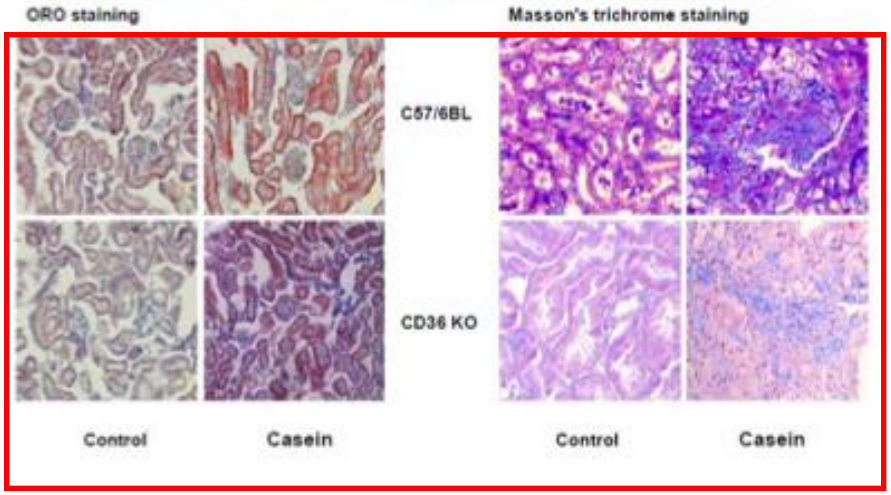
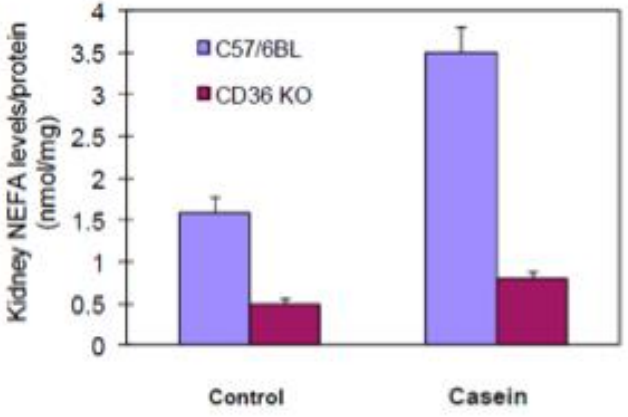
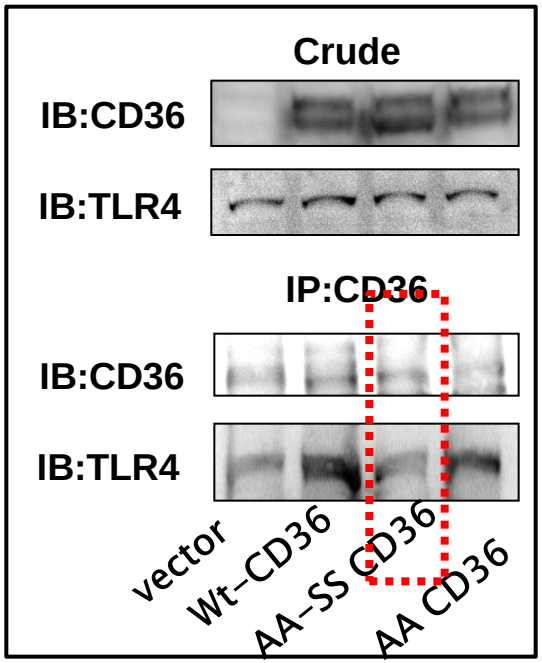


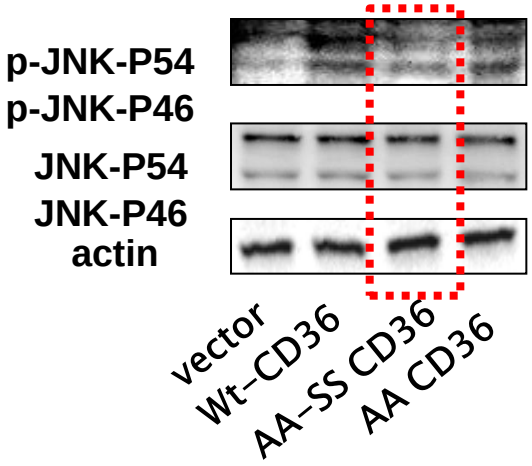
Figure 7. CD36 KO reduces kidney NEFA levels and also response to inflammatory stress

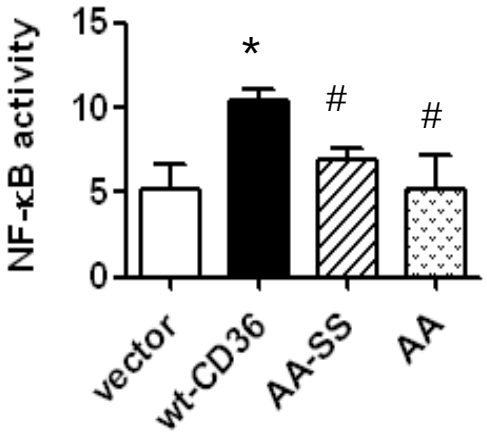


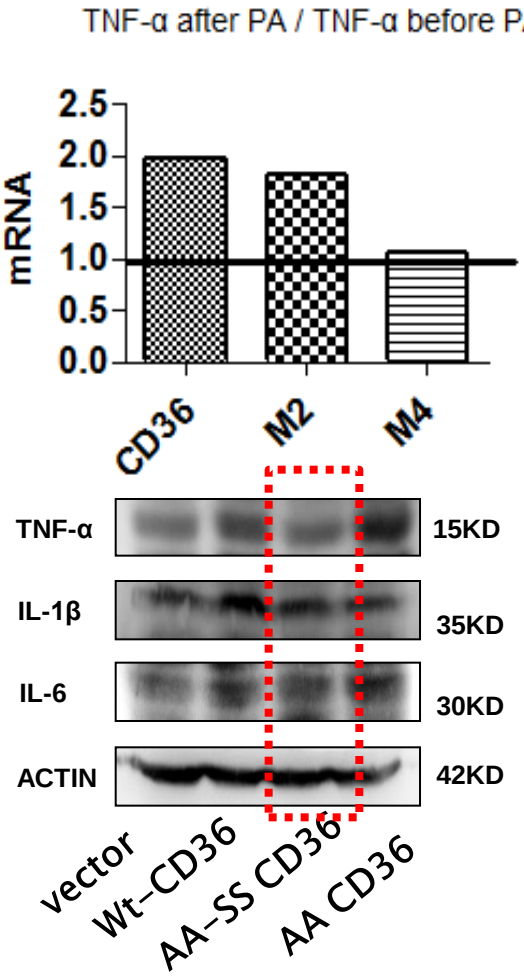
Unpublished data

Palmitoylation influence CD36/TLR4 dimers formation and JNK/NF-kappB inflammatory signaling pathway



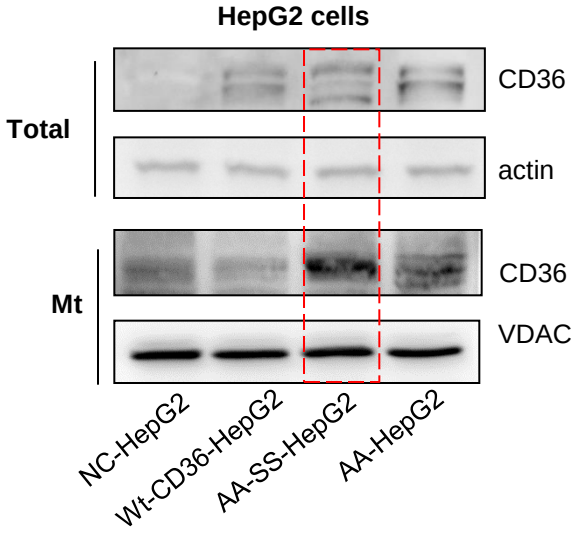


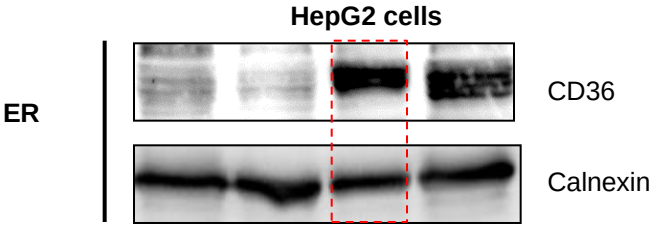


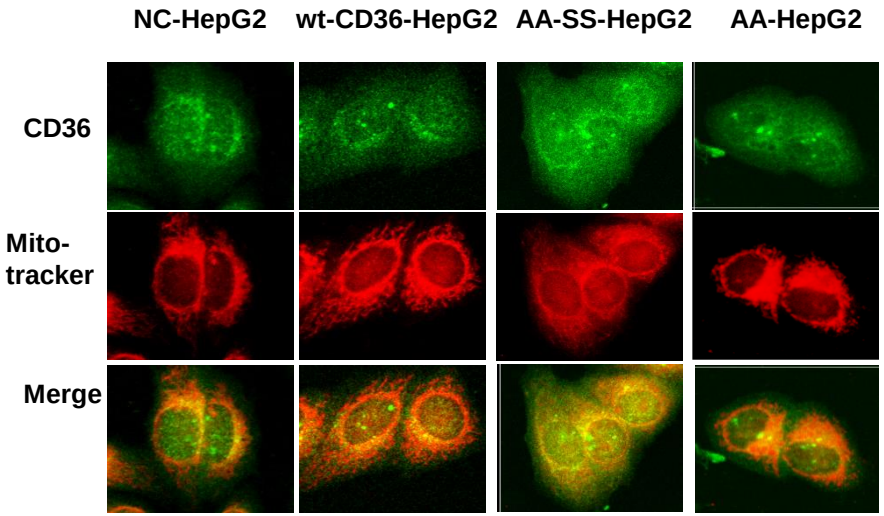


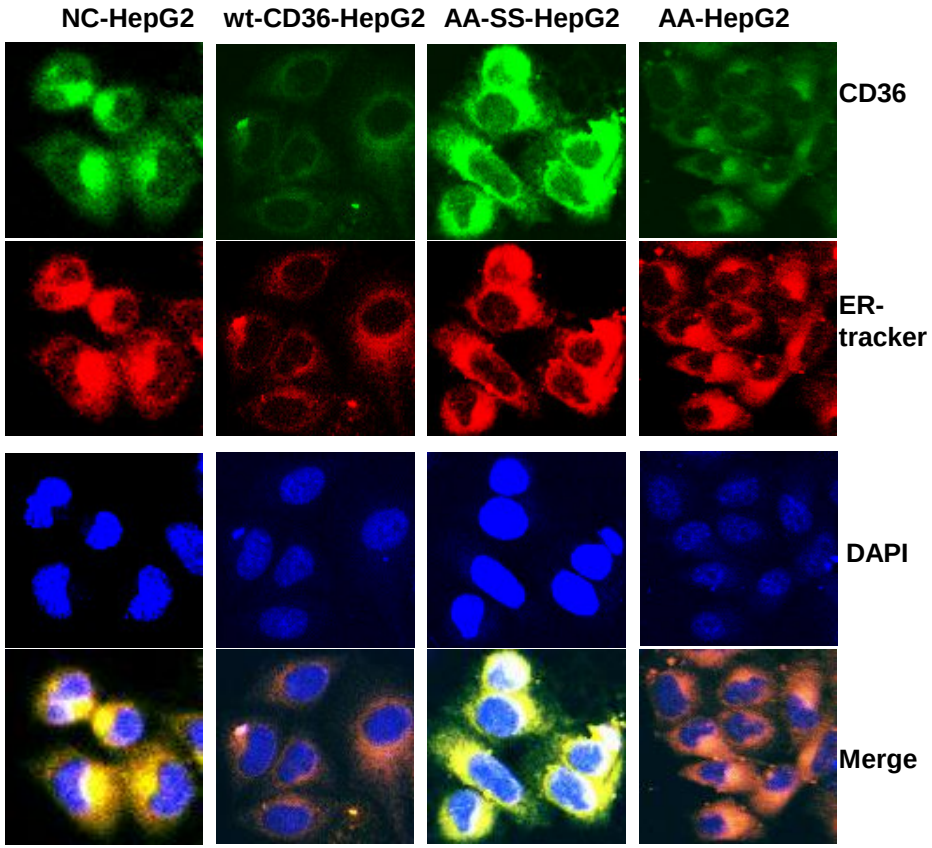
Unpublished data

The absence of palmitoylation regulates FAT/CD36 subcellular localization





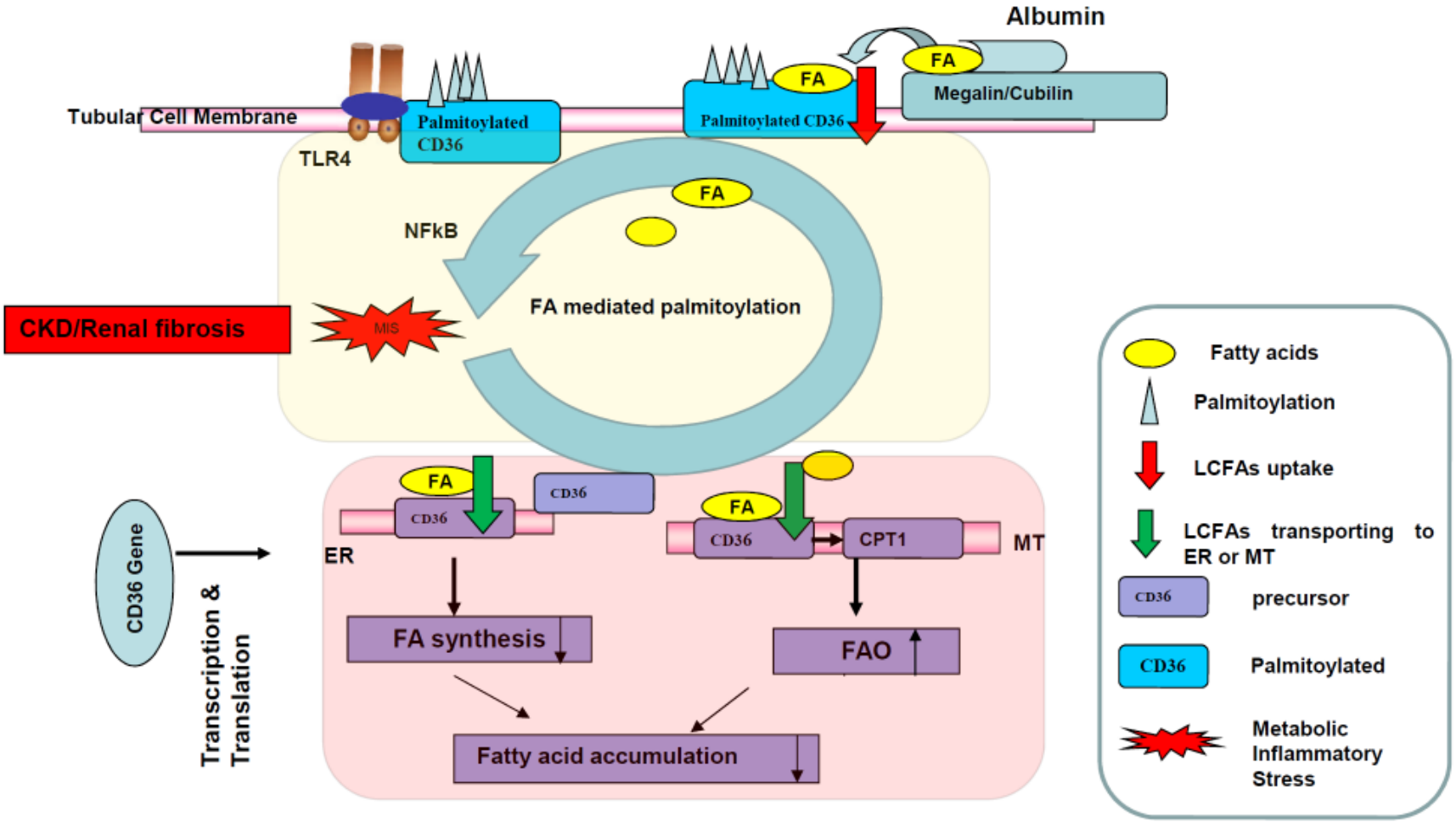




Unpublished data

CD36 lipid redistribution/inflammation ?

Figure 1. Schematic diagram of the proposed hypothesis



Key Original Findings: lipid redistribution

Inflammatory stress causes cholesterol redistribution :

Lancet Diabetes and Endocrinology 2014
Hepatology 48(3), 2008
J Gastroenterol Hepatol 27(5), 2012
Hepatol Int 6(2),2012

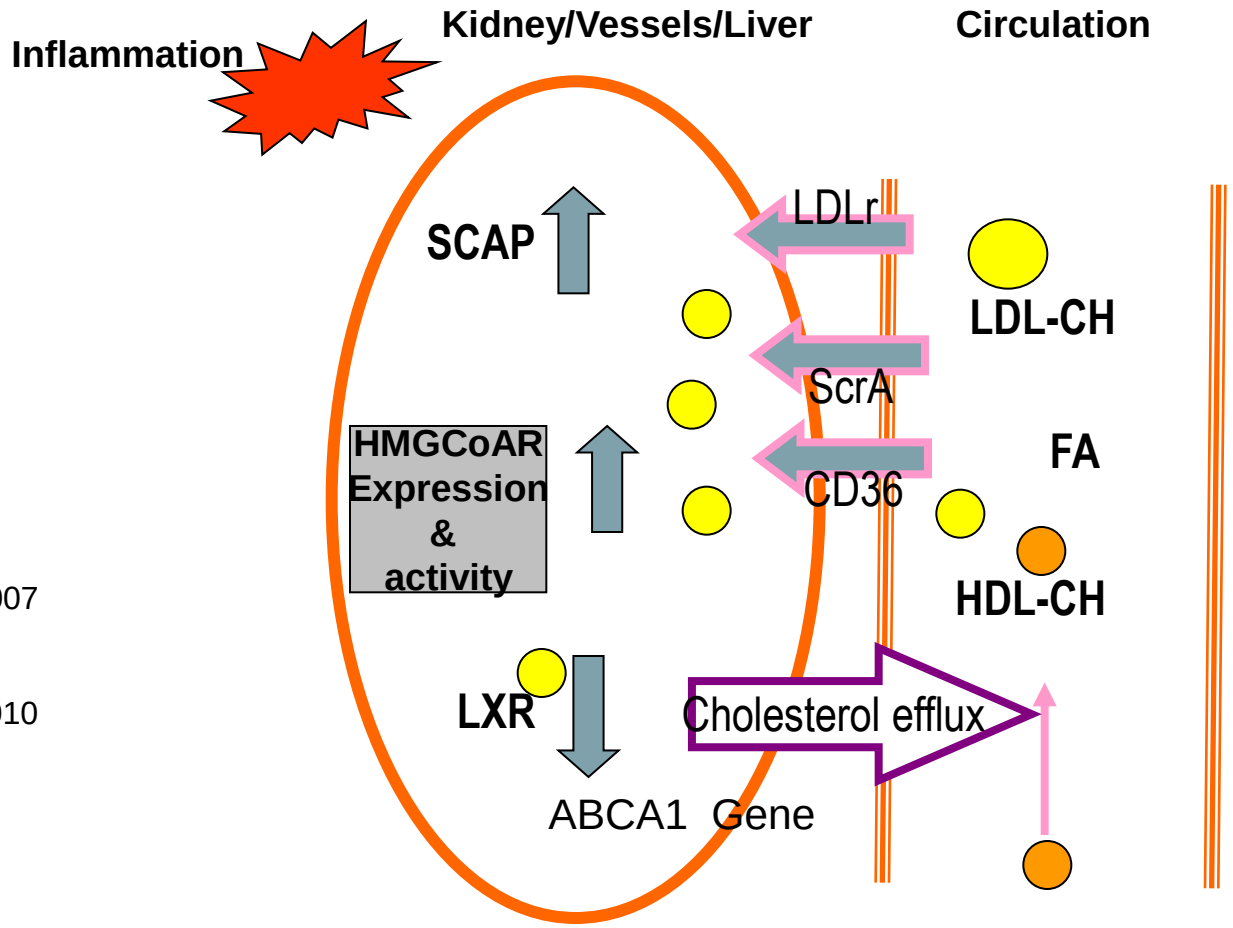
Kidne Int 56(suppl), 1999
Kidney Intl 56(2), 1999
Kidney Int 60(5), 2001
Kidney Int 67(3), 2005
Kidney Int 69 (9):2006
Kidney Int 74 (4), 2008
Kidney Int.78(8): 2010

J Am Soc Nephrol 14(3), 593-600, 2003

Am J Physiol Renal Physiol 293(3), 2007
Am J Physiol Heart Circ Physiol 292(6),2007
Am J Physiol Renal Physiol 289(1), 2005
Am J Physiol Renal Physiol 294(5), 2008
Am J Physiol Heart Circ Physiol 298(6), 2010
Am J Physiol Renal Physiol 301(4), 2011
Am J Physiol Renal Physiol 301(1), 2011

Nephrol Dial Transplant 13(6), 1998
Nephrol Dial Transplant 18 (1), 2003
Nephrol Dial Transplant 23 (6), 2008

Arterioscler Thromb Vasc Biol 26(5), 2006
Arterioscler Thromb Vasc Biol , 2014



Ruan et al **Nature Review Nephrology** 2009;

Lipid nephrotoxicity: promise

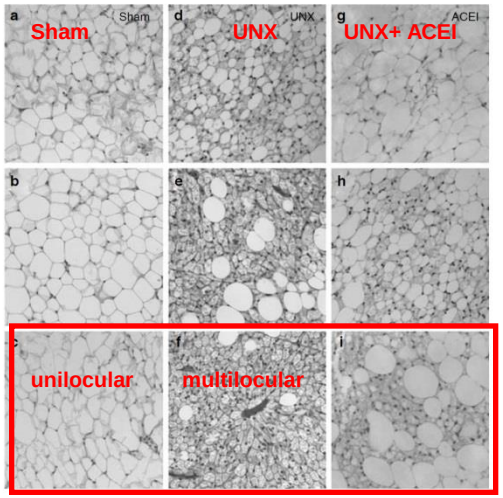
see commentary on page 407

Fat redistribution and adipocyte transformation in uninephrectomized rats

Hai-Lu Zhao[1,5], Yi Sui[1,5], Jing Guan[1], Lan He[1], Xun Zhu[1], Rong-Rong Fan[1], Gang Xu[1], Alice P.S. Kong[1], Chung Shun Ho[2], Fernand M.M. Lai[3], Dewi K. Rowlands[4], Juliana C.N. Chan[1] and Peter C.Y. Tong[1]

[1]Department of Medicine and Therapeutics, The Chinese University of Hong Kong, Hong Kong SAR, China; [2]Department of Chemical Pathology, The Chinese University of Hong Kong, Hong Kong SAR, China; [3]Department of Anatomical and Cellular Pathology, The Chinese University of Hong Kong, Hong Kong SAR, China and [4]Laboratory Animal Services Centre, The Chinese University of Hong Kong, Hong Kong SAR, China

PAS

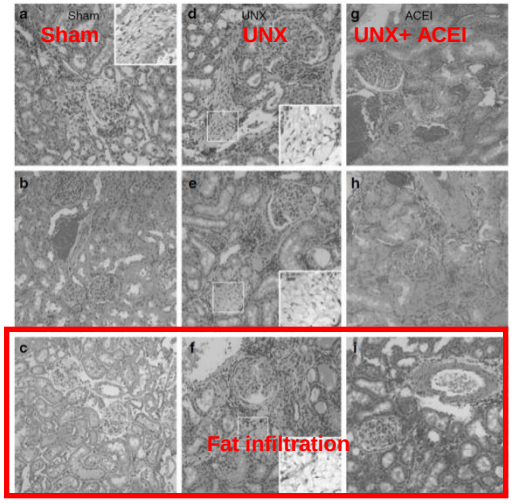


4m

7m

10m

HE



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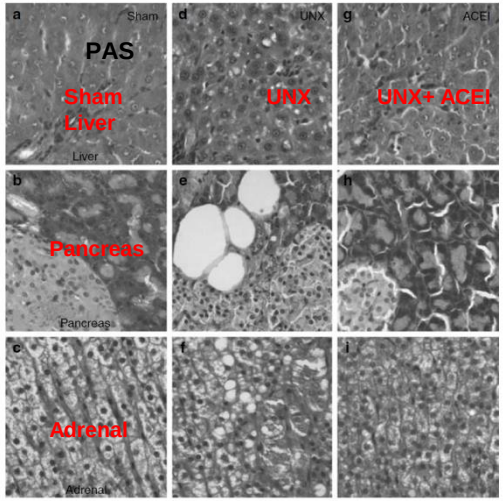
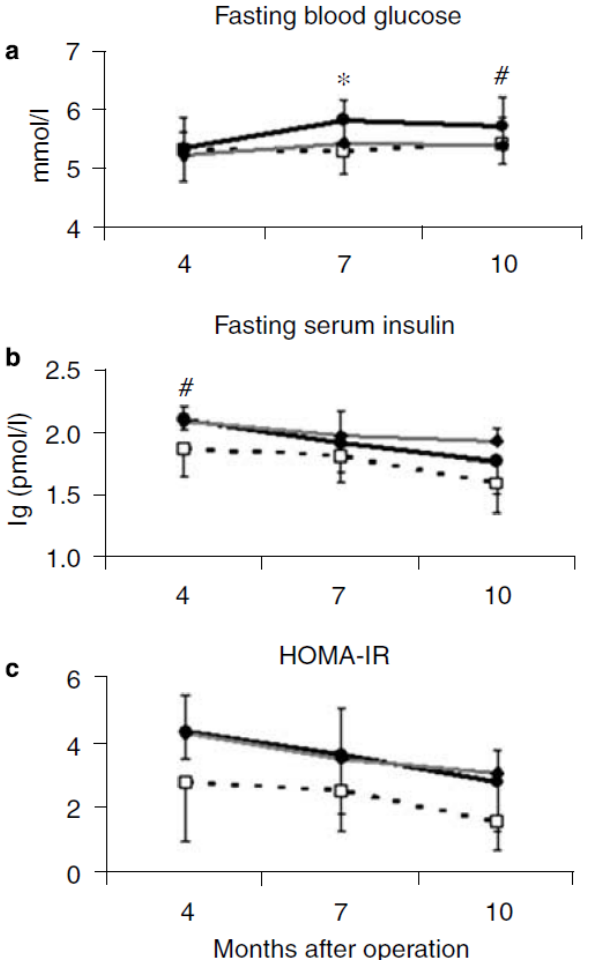


Ectopic fat accumulation



‘Defy the LDL receptor paradigm’ –lipid redistribution

- Cholesterol Sensor SCAP overexpresion
- abnormal translocation from ER to Gogi

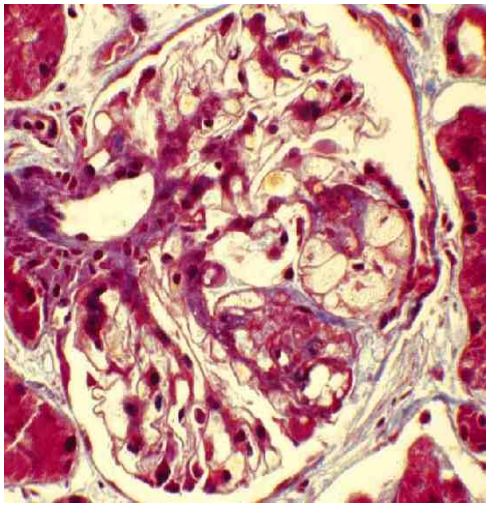
Kidney International, Vol. 60 (2001), pp. 2037–2038

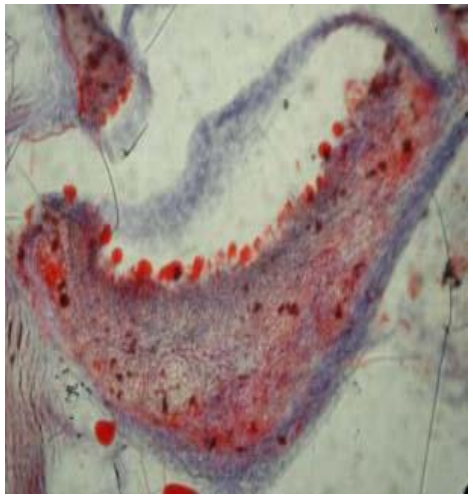
EDITORIAL

Mesangial cells defy LDL receptor paradigm

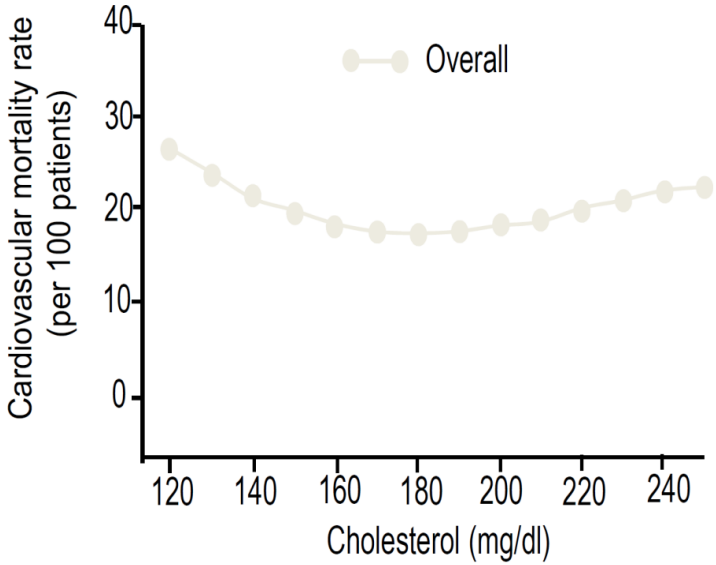
LDL redistribution from circulation to tissues

Lipid accumulation in tissues

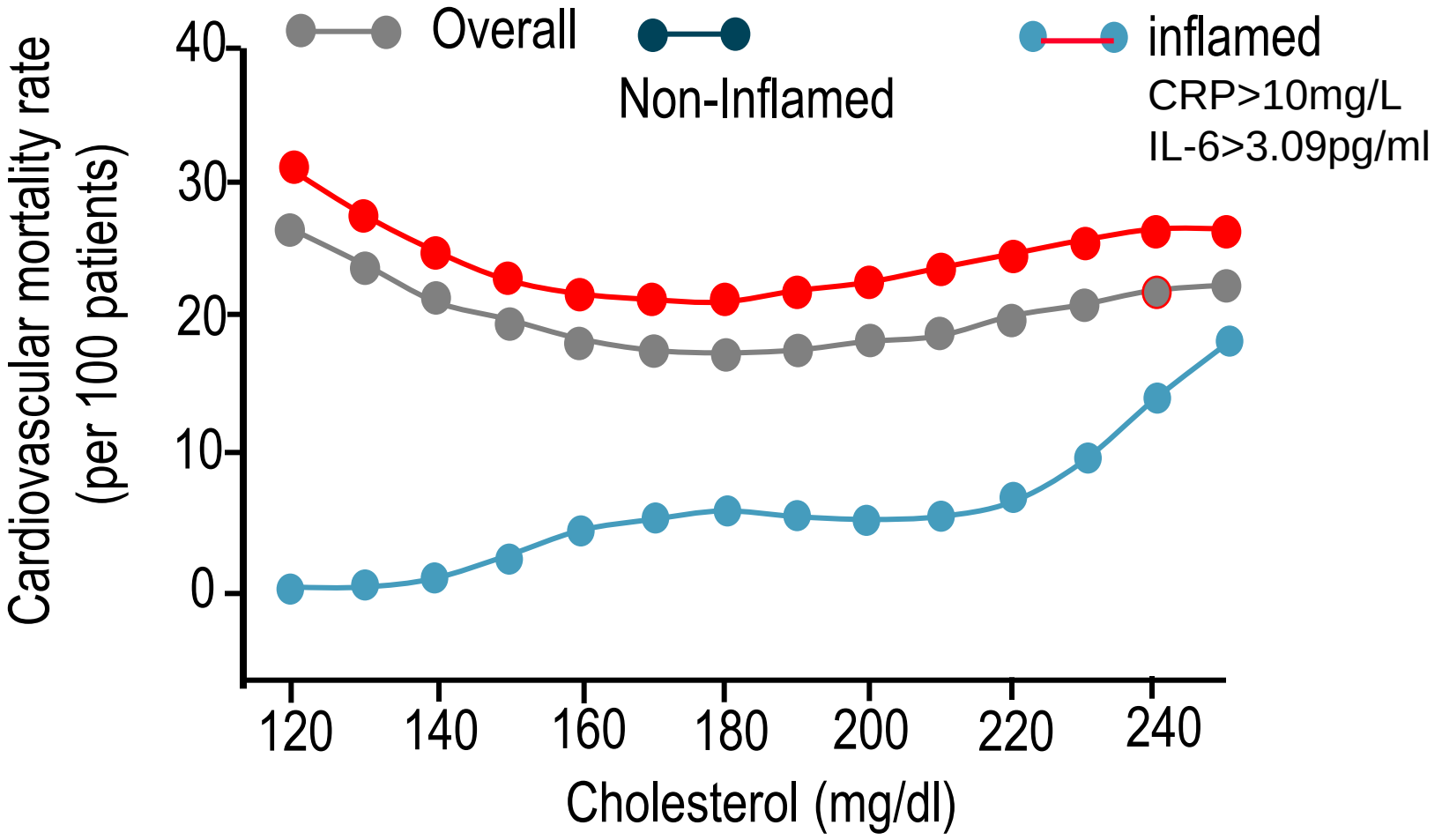




lower LDL cholesterol levels



Inflammation distorts the relationship between blood cholesterol and CV morality



Liu et al, JAMA 2004;291:451-459

脂质肾毒性假说 / 脂肪肾 （350 篇 SCI）

Glomerulo-atherosclerosis

CKD

ORG

Obesity

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VLDL ↑ ↑

VLDL remnants ↑
Small dense LDL ↑

HDL ↓

Ruan et al
Nature Rev Nephrol 2009

Ma, et al **Hepatology 2009**

Inflammation

Obesity-related Glomerulopathy Renal Biopsy Series 1986-2000

- Entry Criteria:
  BMI>30 and biopsy findings of :
  -FSGS with glomerulomegaly(O-FSGS) or
  -Glomerulomegaly alone (O-GM)

- Exclusion Criteria:
  -any other underlying conditions that could cause secondary FSGS(HIV, solitary kidney, sickle cell disease, renal dysplasia, reflux, etc.), diabetic nephropathy and hypertensive nephrosclerosis

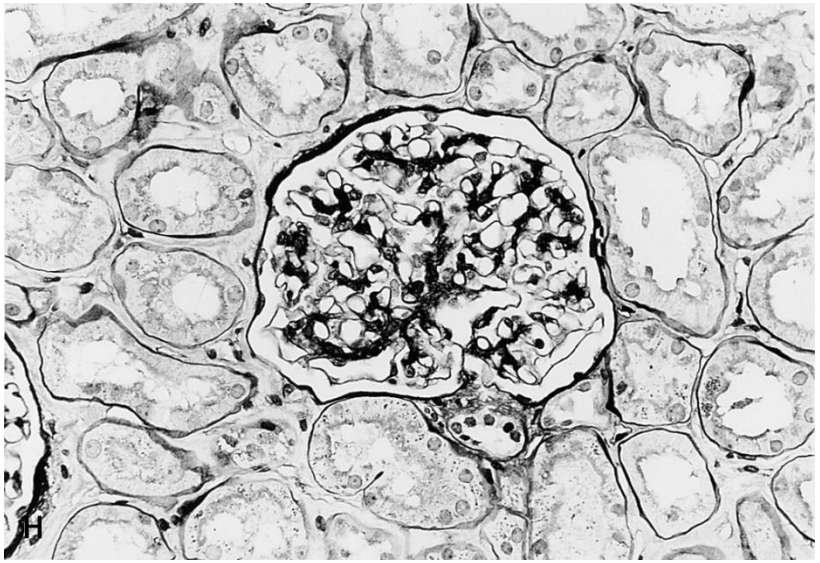
(Kambham et al. KI 59:1498,2001)

Obesity-related Glomerulopathy

ORG

Mean 226um

Age-matched control



Mean 168um

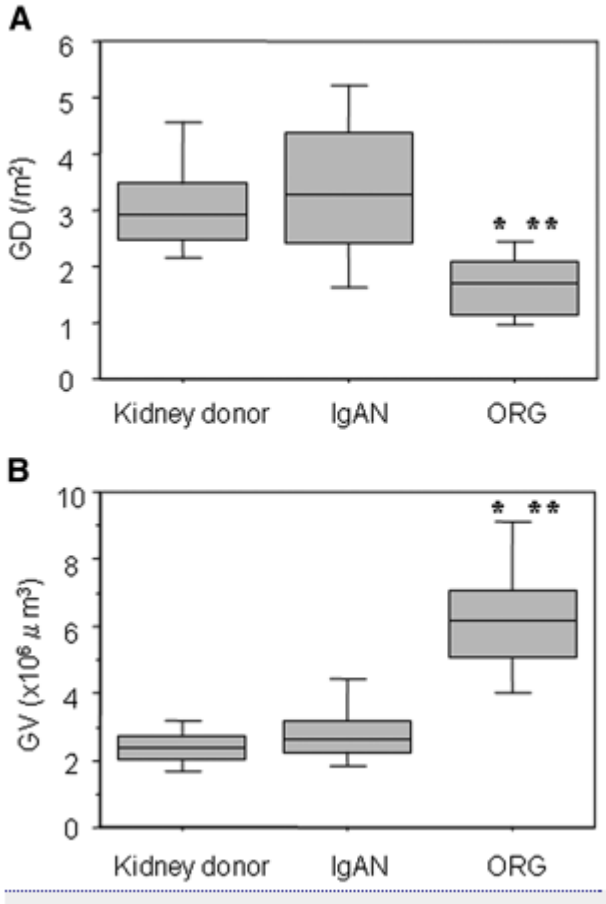
Kambham et al. KI 59:1498,2001

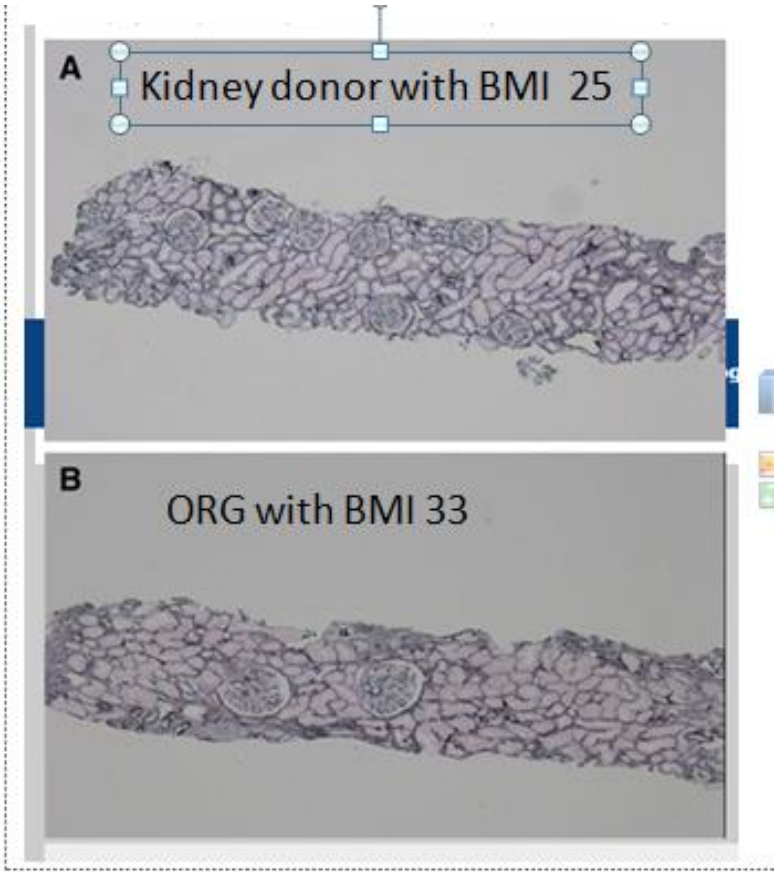
Obesity-related Glomerulopathy (ORG)

Low glomerular density with glomerulomegaly in obesity-related glomerulopathy.

Glom Density

Glom Volume

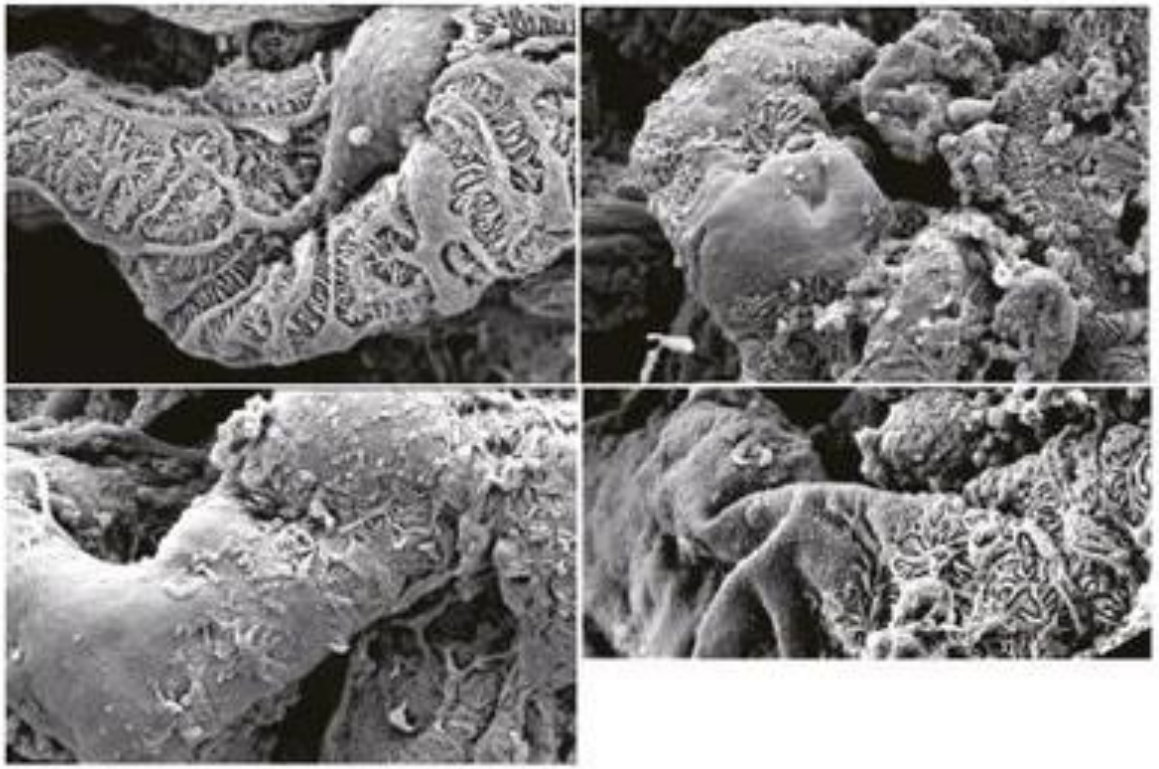




Tsuboi et al.CJASN 2012

Podocyte changes in rat model of obesity-induced FSGS

Failure of podocyte to match glomerular tuft growth in response to growth signaling can trigger FSGS



Scanning EM: areas of intact foot processes and foci of podocyte depletion

Fukuda A et al, JASN 23:1351,2012

Taking home messages

- Obesity associates with dyslipidemia, causing metabolic inflammatory stress;
- CD36 plays important role in mediating inflammatory stress by forming complex with TLR4
- Inflammation causes lipid redistribution, indicating that absolute plasma cholesterol level is not good indicator for risk assessment;

No cholesterol levels are safe if CRP is high

Ruan et al **Nature Review Nephrology** 2009;

Acknowledgments

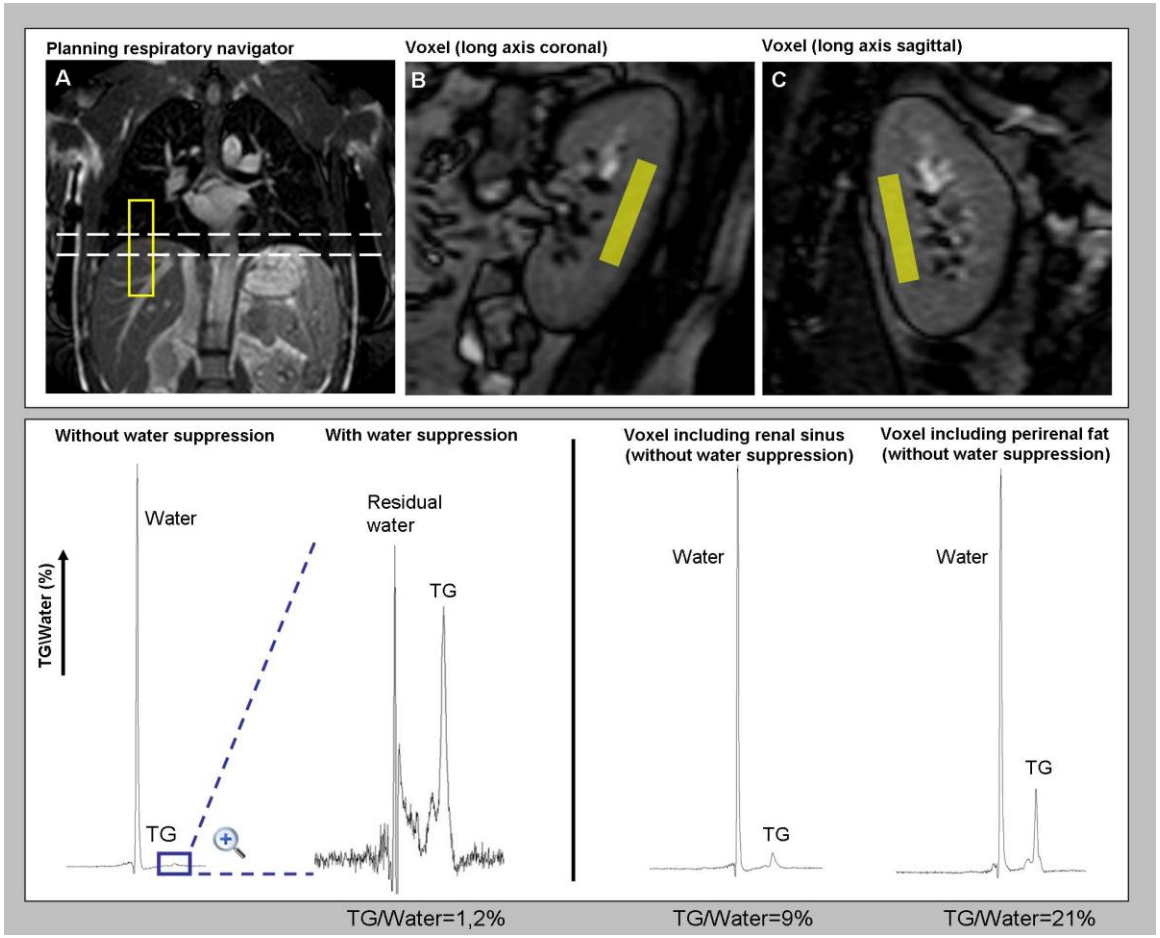
Renal-oriented Lipid Research (Moorhead Trust):

- **UCL-CQMU Centre for Lipid Research (active)**
  - Founded in 2006
  - Designated as A Key Laboratory of MOE and A Joint Laboratory for Lipid Res in UCL-CQMU
  - 1 Metabolic disease animal centre (12 transgenic lines on breeding)
  - 5 Lipid Research Collaboration Groups cross China (16 UCL Fellows trained in RF)
  - ISLT2006, 2009, and 2012.
  - 54 papers joint published since 2006
- **More (under discussion)**
  - Genetic study/Biobank/Inflammation/Renal Physiology
  - Chinese Society of Renal Physiology: ISN Forefront symposium 2015
  - International Hospital (Royal Free)

Grants

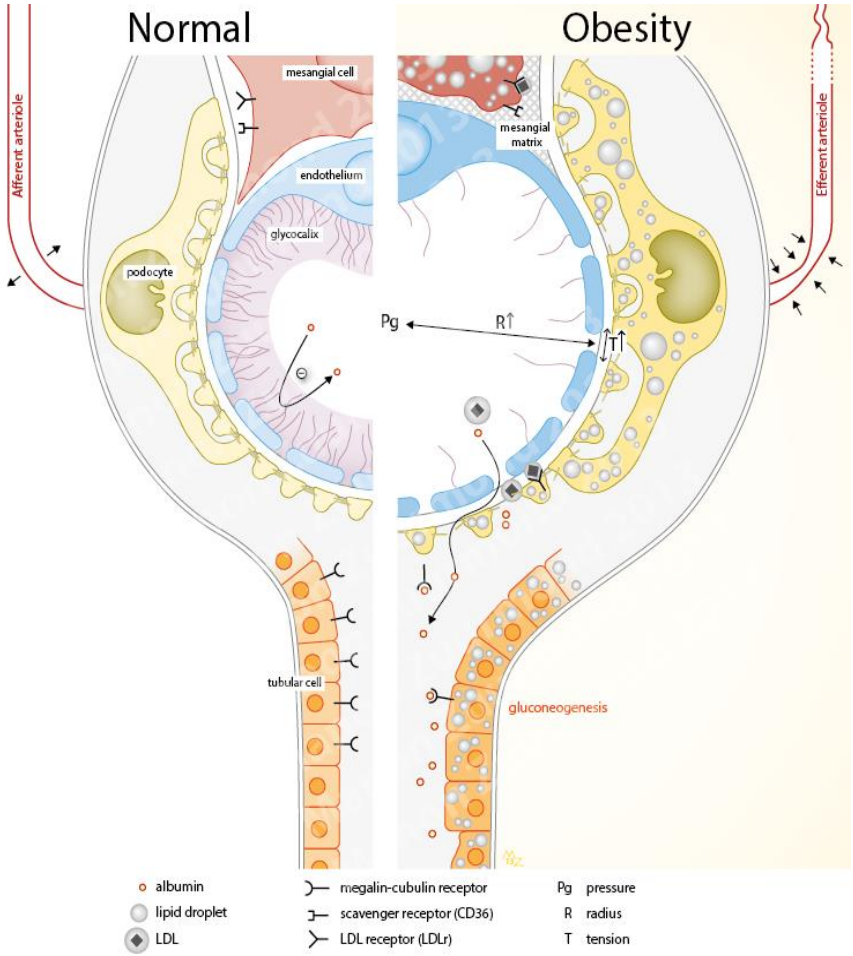
UK: Kidney Research UK, Moorhead Trust; China: 973 (3) , NSFC programme grants (2)

Lipid nephrotoxicity: promise



Hammer S. PloS one 2013;8(4):e62209.
Rutledge JC. Nat Rev Nephrol 2010;6(6):361-370.

Lipid nephrotoxicity: mechanisms?



Review

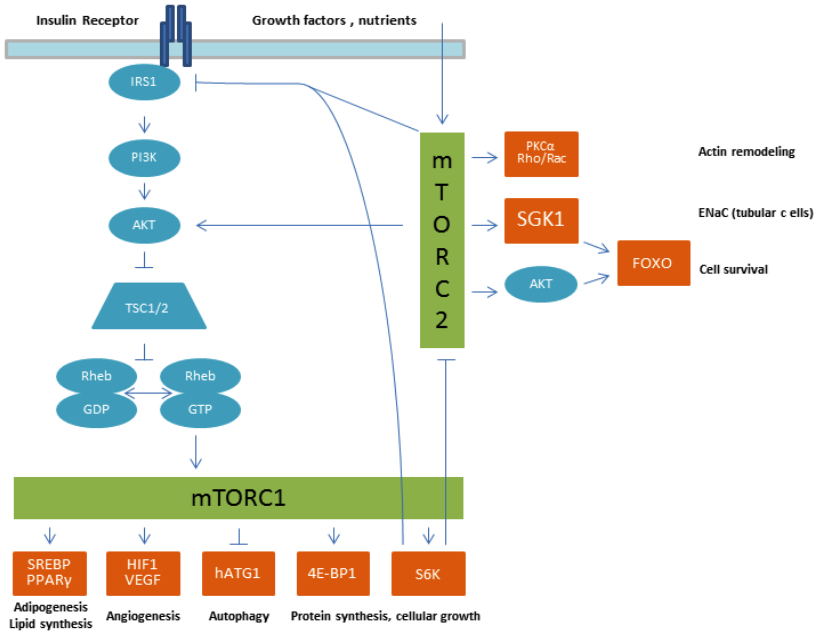
Fatty kidney: emerging role of ectopic lipid in obesity-related renal disease

Aiko P J de Vries, Piero Ruggenenti, Xiong Z Ruan, Manuel Praga, Josep M Cruzado, Ingeborg M Bajema, Vivette D D'Agati, Hildo J Lamb, Drazenka Pongrac Barlovic, Radovan Hojs, Manuela Abbate, Rosa Rodriquez, Carl Erik Mogensen, Esteban Porrini, for the ERA-EDTA Working Group Diabesity

The global increase in chronic kidney disease (CKD) parallels the obesity epidemic. Obesity conveys a gradual but independent risk of progression of CKD that seems irrespective of the underlying nephropathy. Obesity has been associated with a secondary focal segmental glomerulosclerosis coined obesity-related glomerulopathy (ORG). Pathways through which obesity might cause renal disease are not well understood, and early clinical biomarkers for incipient ORG or renal relevant obesity are currently lacking. Recent human and experimental studies have associated ectopic lipid accumulation in the kidney (fatty kidney) with obesity-related renal disease. There is enough growing insight that ectopic lipid—the accumulation of lipid in non-adipose tissue—is associated with structural and functional changes of mesangial cells, podocytes, and proximal tubular cells to propose the development of ORG as a maladaptive response to hyperfiltration and albuminuria. Recent advances in metabolic imaging might validate ectopic lipid as a biomarker and research aid, to help translate novel therapeutics from experimental models to patients.

Lancet Diabetes Endocrinol 2014; 2: 417–26

Department of Nephrology (A P J de Vries MD), Department of Pathology (I M Bajema MD), and Department of Radiology (H J Lamb MD), Leiden University Medical Center and Leiden University, Leiden, Netherlands; IRCCS—Istituto di Ricerche Farmacologiche Mario Negri, Clinical Research Center for Rare Diseases "Aldo e Cele Daccò".



脂质肾毒性假说 / 脂肪肾 （350 篇 SCI）

Glomerulo-atherosclerosis

CKD

Fatty Kidney

LIPID NEPHROTOXICITY IN CHRONIC PROGRESSIVE GLOMERULAR AND TUBULO-INTERSTITIAL DISEASE

J. F. MOORHEAD M. K. CHAN
M. EL-NAHAS Z. VARGHESE

Department of Nephrology and Transplantation, Royal Free Hospital, London NW3 2QG

Moorhead & Varghese et al
Lancet 1982

Aiko et al.
Lancet Diabetes and Endocrinology 2014

Obesity

VLDL ↑ ↑

VLDL remnants ↑
Small dense LDL ↑

HDL ↓

Ruan et al
Nature Rev Nephrol 2009

Ma, et al **Hepatology 2009**

Inflammation

NAFLD

Lipid nephrotoxicity:

LIPID NEPHROTOXICITY IN CHRONIC PROGRESSIVE GLOMERULAR AND TUBULO-INTERSTITIAL DISEASE

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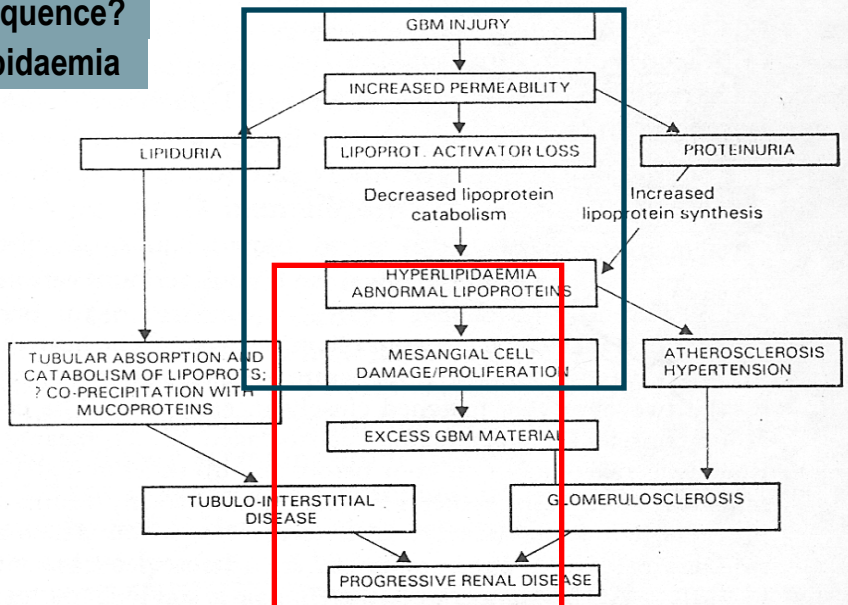
Department of Nephrology and Transplantation, Royal Free Hospital, London NW3 2QG

THE LANCET, DECEMBER 11, 1982

Consequence?

Renal disease causes dyslipidaemia



Proposed mechanisms for the pathogenesis of lipid-induced glomerular atherosclerosis and tubulo-interstitial damage in chronic progressive renal disease.

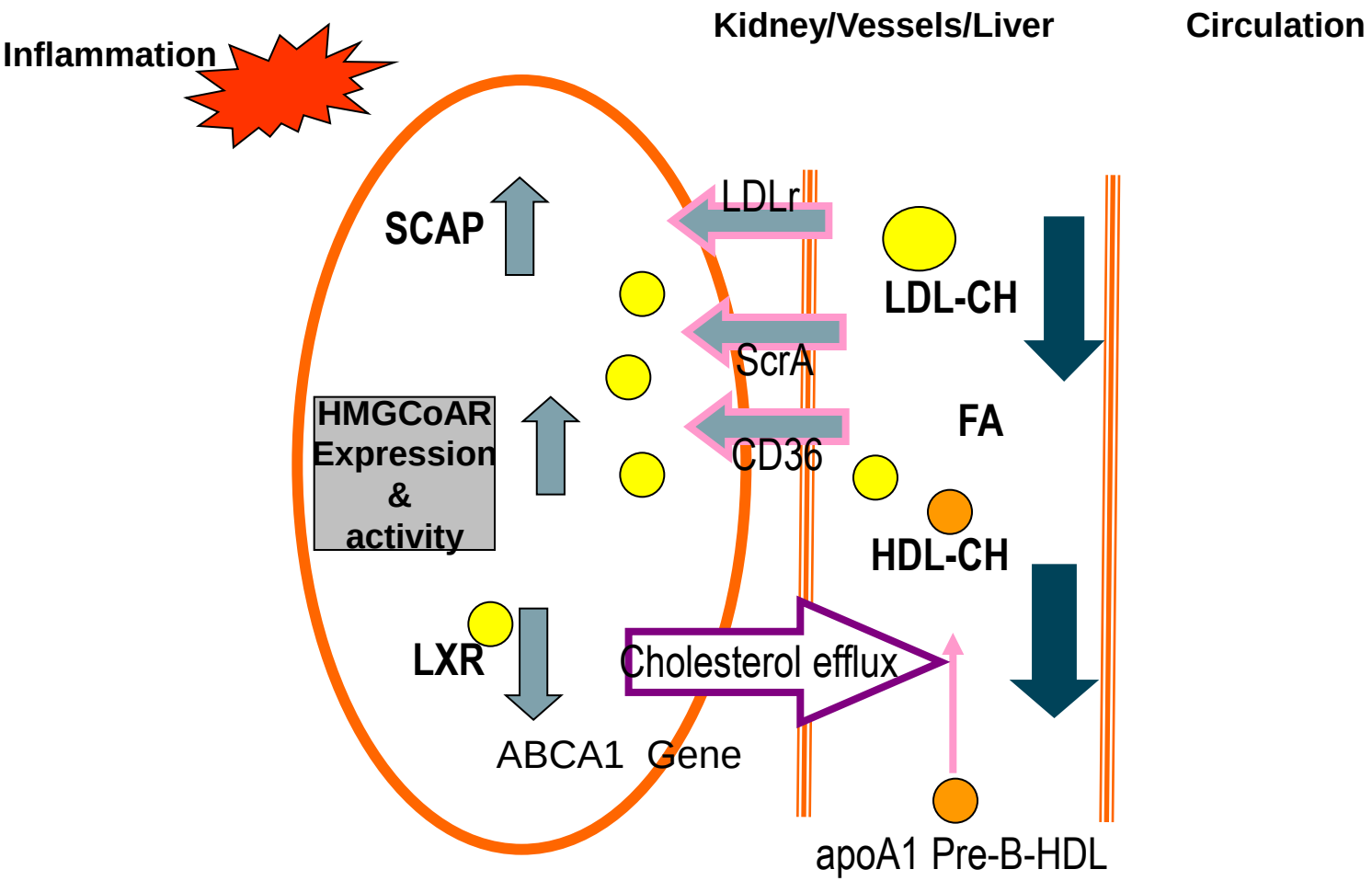
Cause?

Dyslipidaemia causes renal injury

NR/ABCA1 and lipid redistribution?

Inflammatory stress causes cholesterol redistribution :

(300 publications since 1982)



Ruan et al **Nature Review Nephrology** 2009;

脂质肾毒性假说 / 脂肪肾 （350 篇 SCI）

Glomerulo-atherosclerosis

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Inflammation

NAFLD

Insights from Gene Expression Profiles of the Glomeruli Derived from Renal Biopsy Samples

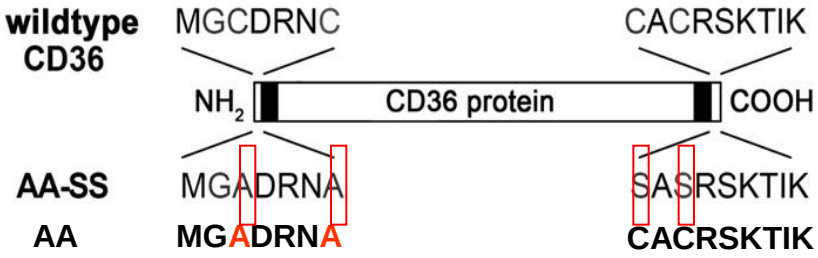
TABLE 4. The top decreased genes in the glomeruli of ORG patients compared with controls (>2-fold; $P < 0.01$)

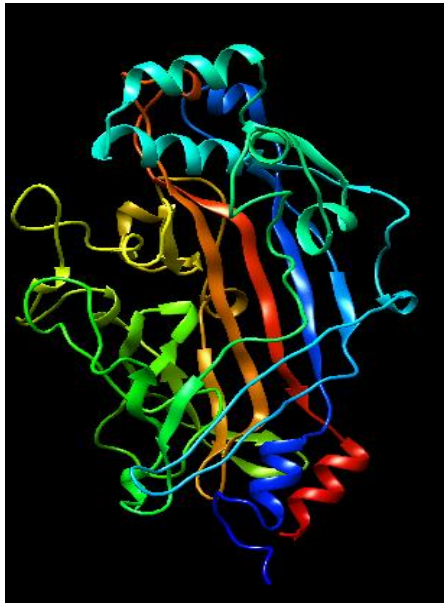
Accession no.	Fold[1]	Gene name	Function
NM_000596	−2.12	IGF-binding protein 1	Insulin function
AB028973	−3.56	Myelin transcription factor 1	Transcription factor
D13891	−2.98	Inhibitor of DNA binding 2	Transcription factor
NM_003453	−2.85	Zinc finger protein 198	Transcription factor
BC002704	−4.21	Signal transducer and activator of transcription 1	Signal transduction
AF040752	−2.06	G protein-coupled receptor kinase 6	Signal transduction
NM_001827	−3.18	CDC28 protein kinase 2	Cell cycle
NM_002048	−2.01	Growth arrest-specific 1	Cell cycle
NM_001621	−3.91	Aryl hydrocarbon receptor	Apoptosis process
NM_003816	−2.34	A disintegrin and metalloproteinase domain 9	Membrane protein
BC000687	−2.62	Translocation associated membrane protein 1	Membrane protein
U48734	−4.32	Non-muscle alpha-actinin	Cytoskeleton molecule
NM_003174	−2.13	Supervillin	Cytoskeleton molecule
BC000914	−4.65	Splicing factor, arginine/serine-rich 3	mRNA splicing
NM_003020	−2.34	Secretory granule, neuroendocrine protein 1	Enzyme activator
NM_000942	−2.98	Peptidylprolyl isomerase B	Protein folding

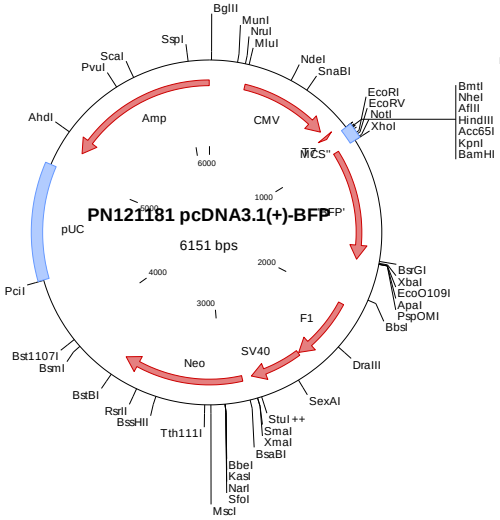
[1]Ratio of average expression level (normalized data) in glomeruli from the controls compared with that from the ORG patients. The minus sign represents down-regulation of the genes.

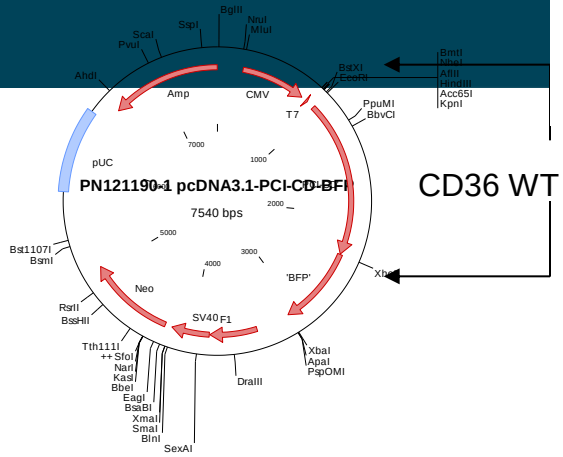
Wu et al. Endocrinol 147:44,2006

CD36及棕榈酰化突变荧光载体的构建



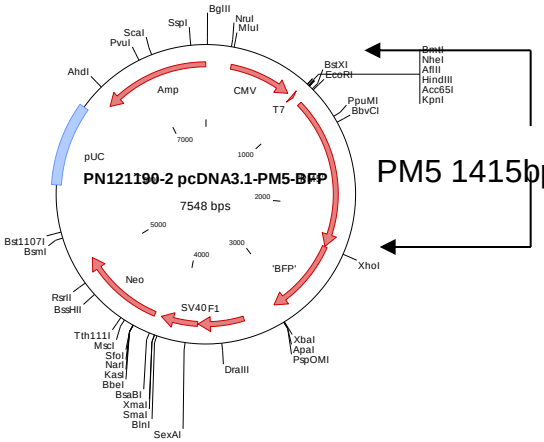






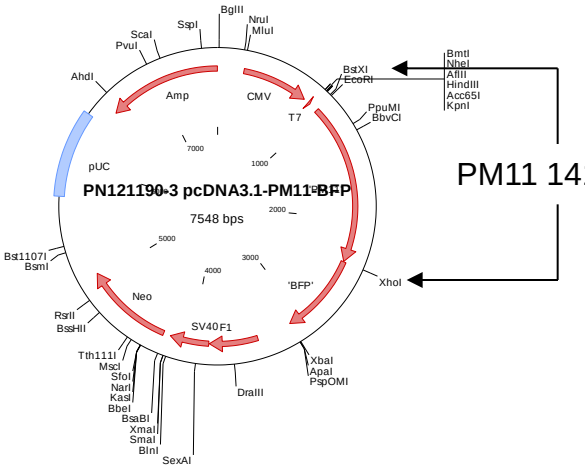
CD36 WT 1415bp

WT



PM5 1415bp (2位点突变)

AA



PM11 1415bp (4位点突变)

AA-SS

Etiologic Classification of FSGS

I. Primary(Idiopathic) FSGS Secondary to putative permeability factor

II. Secondary FSGS

Famillal/Genetic
Mutations in α-actin4
Mutations in podocin
Mutations in nephrin
Mutations in TRPC6

Vrius-Associated
HIV-1（"HIV-associated nephropathy"）
Parvovirus B-19

Drug-Induced
Heroin ("Heroin nephropathy")
Interferon
Lithium
Pamidronate
Anabolics

Mediated by Adaptive
Structural-Functional Responses

Reducd renal mass
Oligomeganephronia
Unllateral renal agenesis
Renal dysplasia
Low birth weight
Sequelato cortical necrosis
Surgical renal ablation
Reflux Nephropathy
Any advanced renal disease with reduction
In functioning nephrons

Initially normal renal mass
Hypertension
Atheroemboll or other acute vaso-occlusive processes
Obesity
Cyanotic congenital heart disease
Sickle cell anemia

Kawasaki et al. Pediatrics Intern, 2014

Relationship between body weight and glomerular volume