Diabetic nephropathy:
Role of metabolic nuclear receptors
(糖尿病肾病：核受体的作用）

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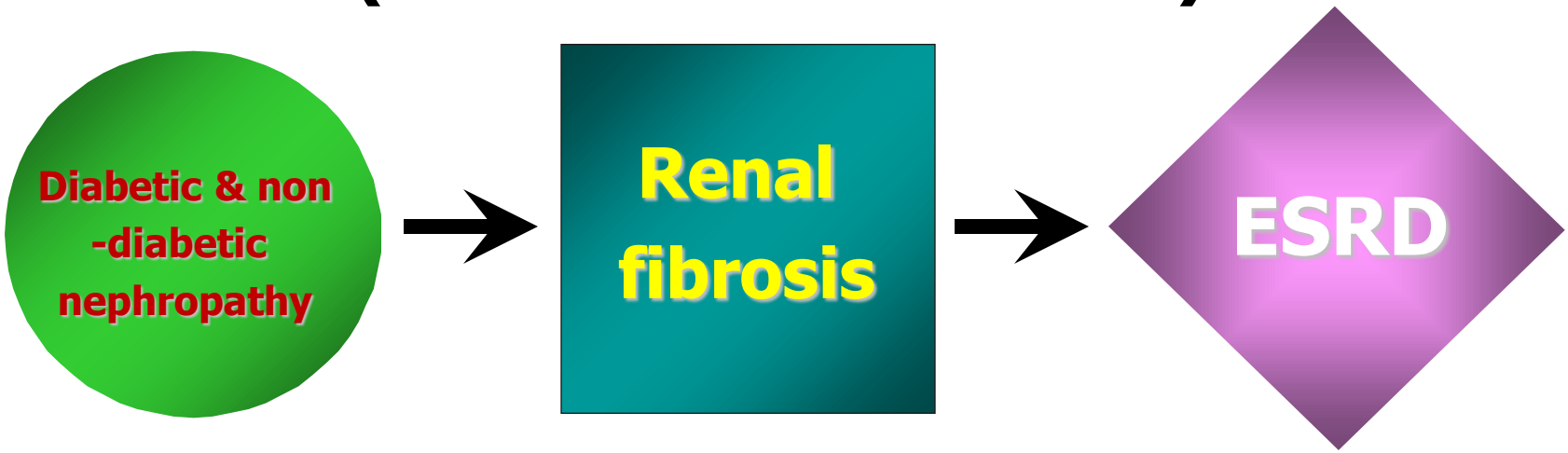
肾脏纤维化 (Renal Fibrosis)

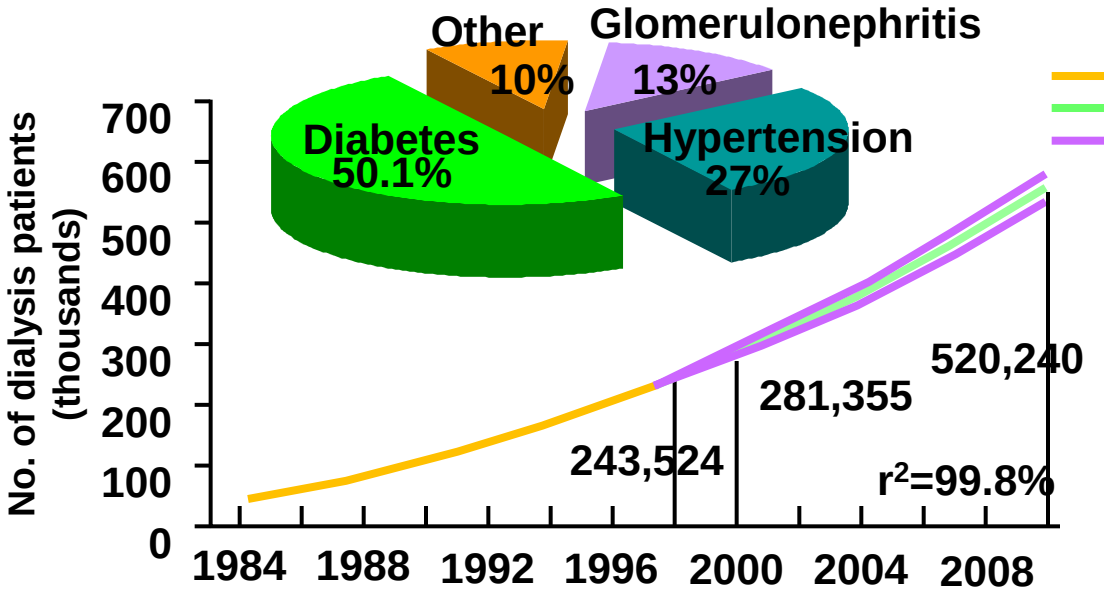
肾脏纤维化是各种不同病因的慢性肾脏疾病进展到终末期肾病的共同病理过程。（**Renal fibrosis is the common pathophysiological basis of all-cause end-stage renal disease, with constant loss of functional nephron, glomerular and tubulointerstitial fibrosis.**）

其主要病理改变为正常肾单位的丢失，大量成纤维细胞的增生和细胞外基质的产生和堆积而导致肾小球硬化、肾小管间质纤维化，最终肾脏功能丧失。

目前对肾脏纤维化的发病机制尚缺乏全面认识，因此深入研究其发病机制和防治措施，已成为十分急迫的问题。

慢性肾病进程
(Time-course of CKD)

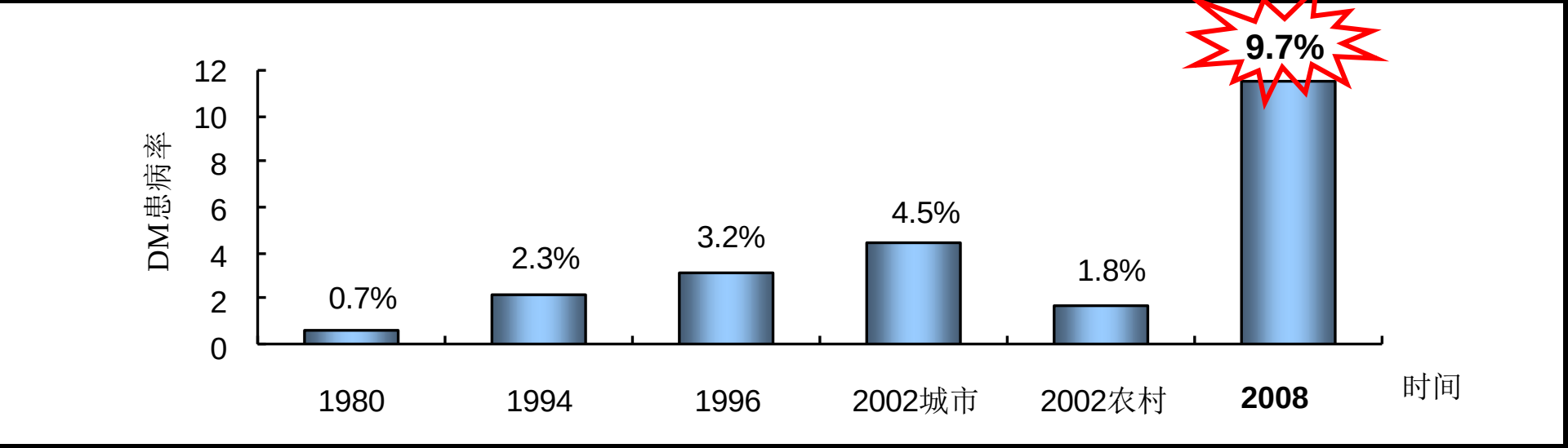




Diabetes is the leading cause of ESRD.

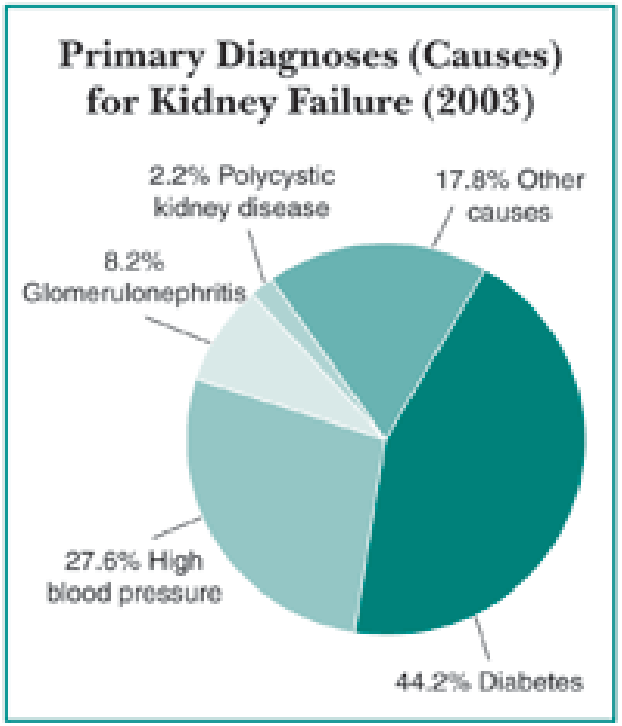
Background

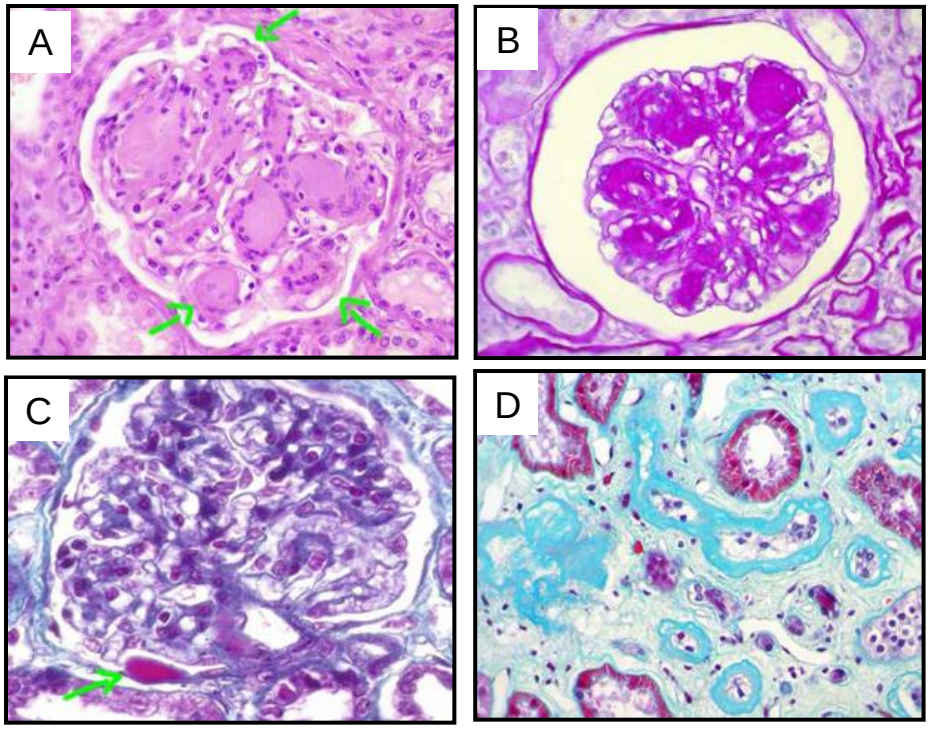
More than 150 million diabetic patients and 250 million pre-diabetic population in China.



Yang WY, Lu JM, Weng JP, et al. Prevalence of Diabetes among Men and Women in China. NEJM, 2010; 362: 1090-1101

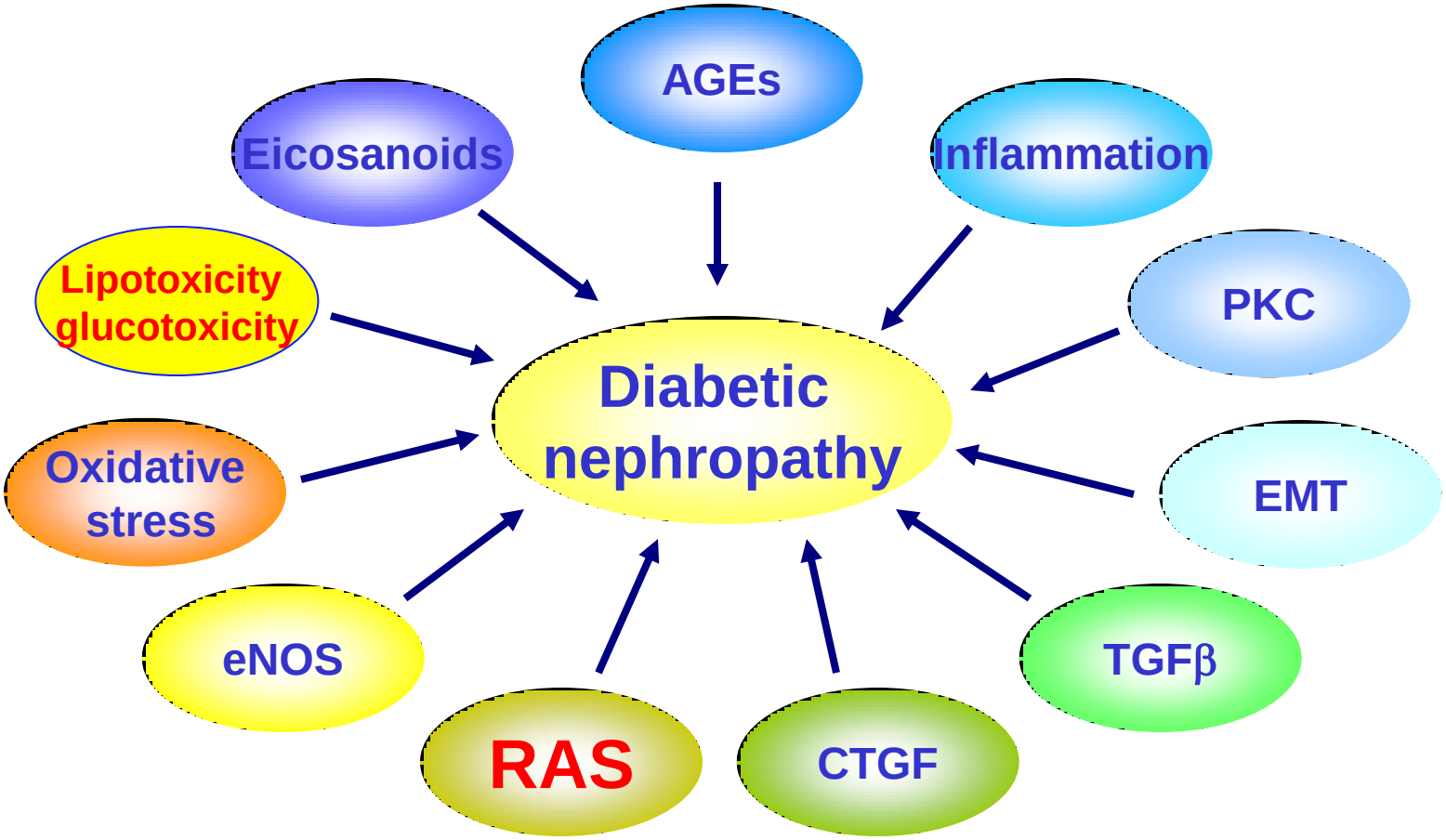
Diabetic nephropathy is the leading cause of end-stage renal disease (ESRD)



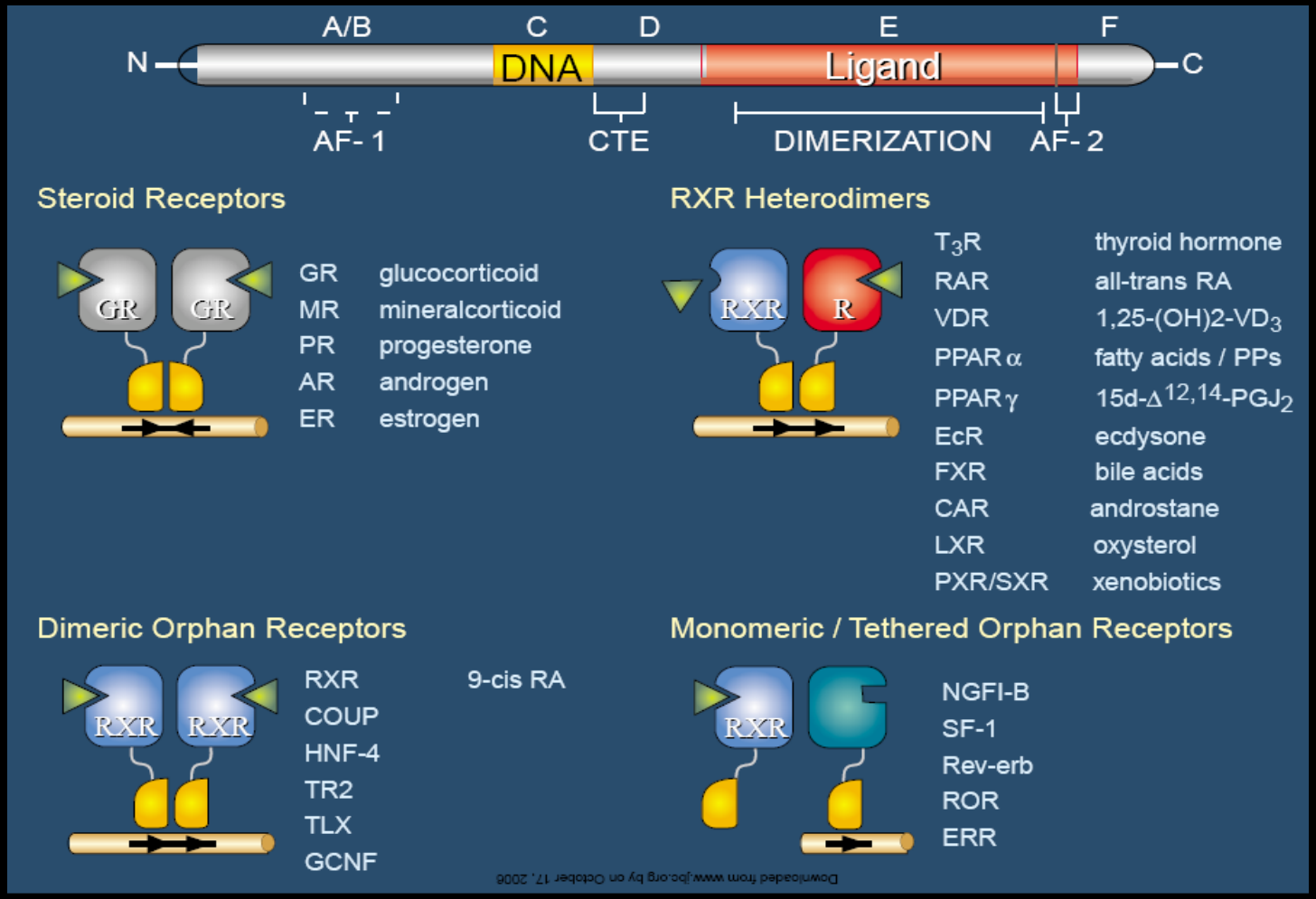


Kimmelstiel-Wilson nodules Tubulointerstitial fibrosis

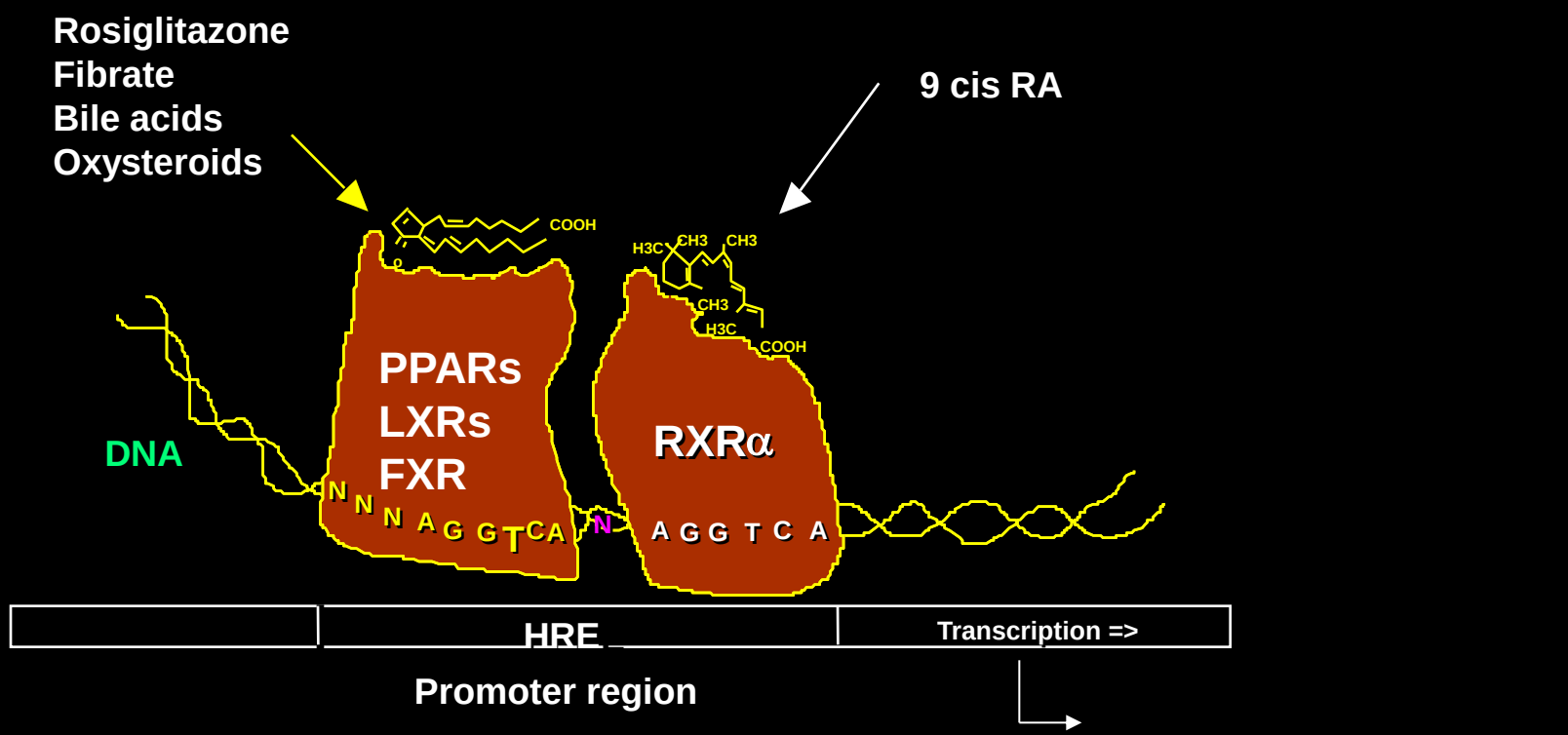
Multiple mechanisms are involved in the pathogenesis of diabetic nephropathy



核受体超家族成员
The superfamily of nuclear receptors



Metabolic Nuclear Receptors: Therapeutic Targets for type 2 Diabetes and Its Renal Complication?



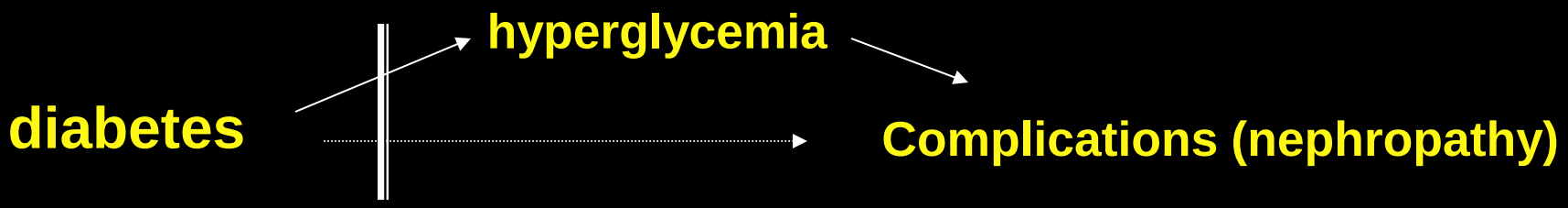
Adipogenesis
Insulin sensitivity
Lipid metabolism
Antiinflammation
Vascular tone regulation
Cell growth and differentiation

PPARγ agonists including rosiglitazone and pioglitazone and PPARα activator such as fenofibrate have been widely used for treating patient with type 2 diabetes and hyperlipidemia.

LXR and FXR ligands also show potentials in treating metabolic disorders including type 2 diabetes and dyslipidemia.

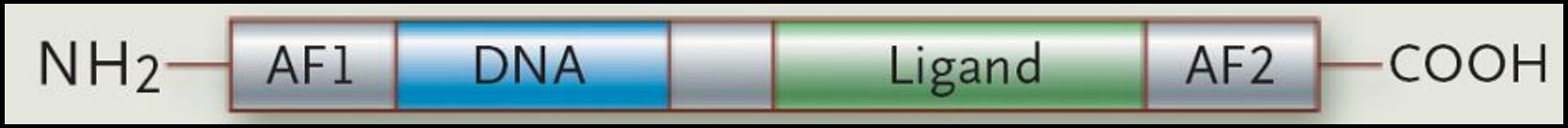
Could they also ameliorate the renal complications of diabetes mellitus via both systemic and direct effects?

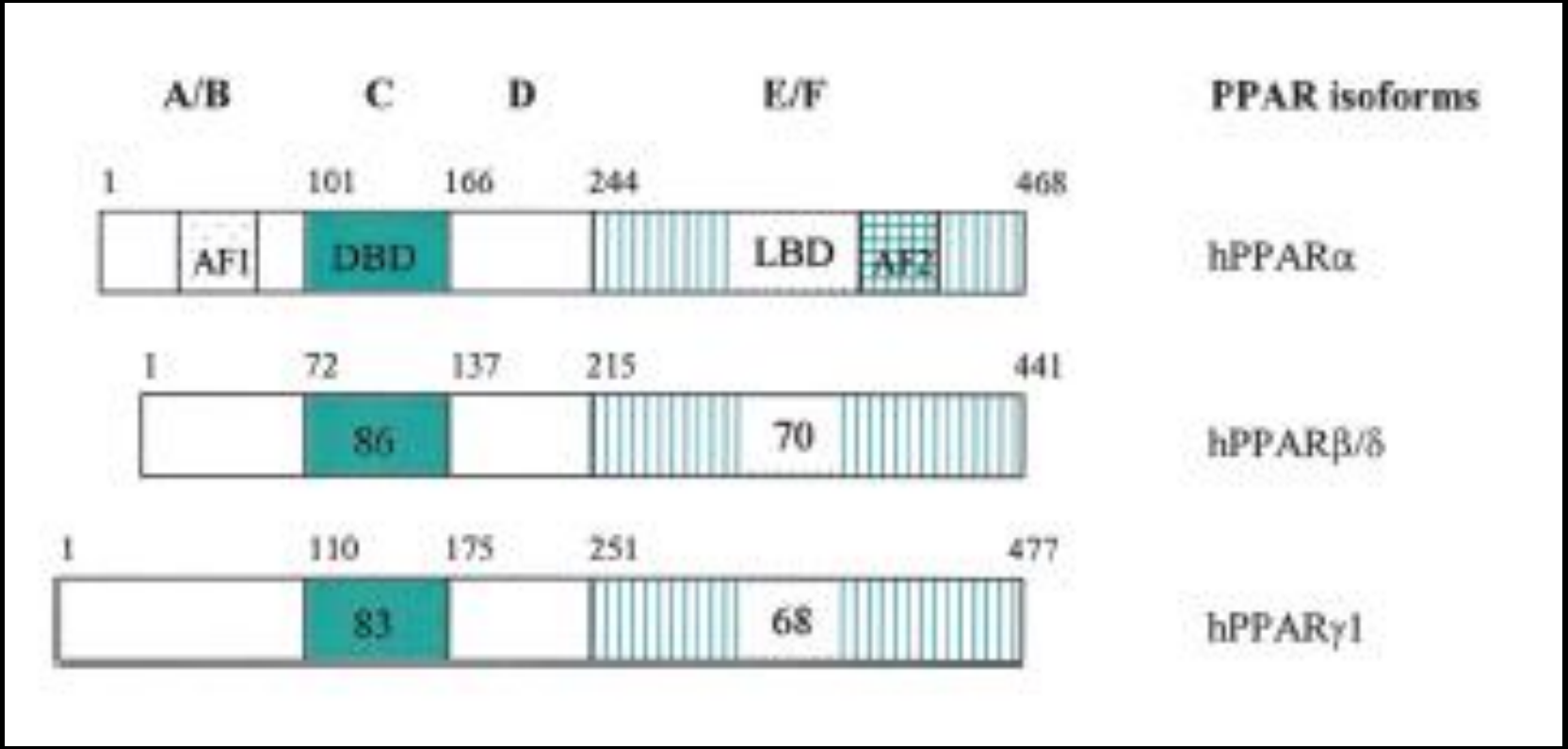
PPAR ligands
LXR ligands
FXR ligands



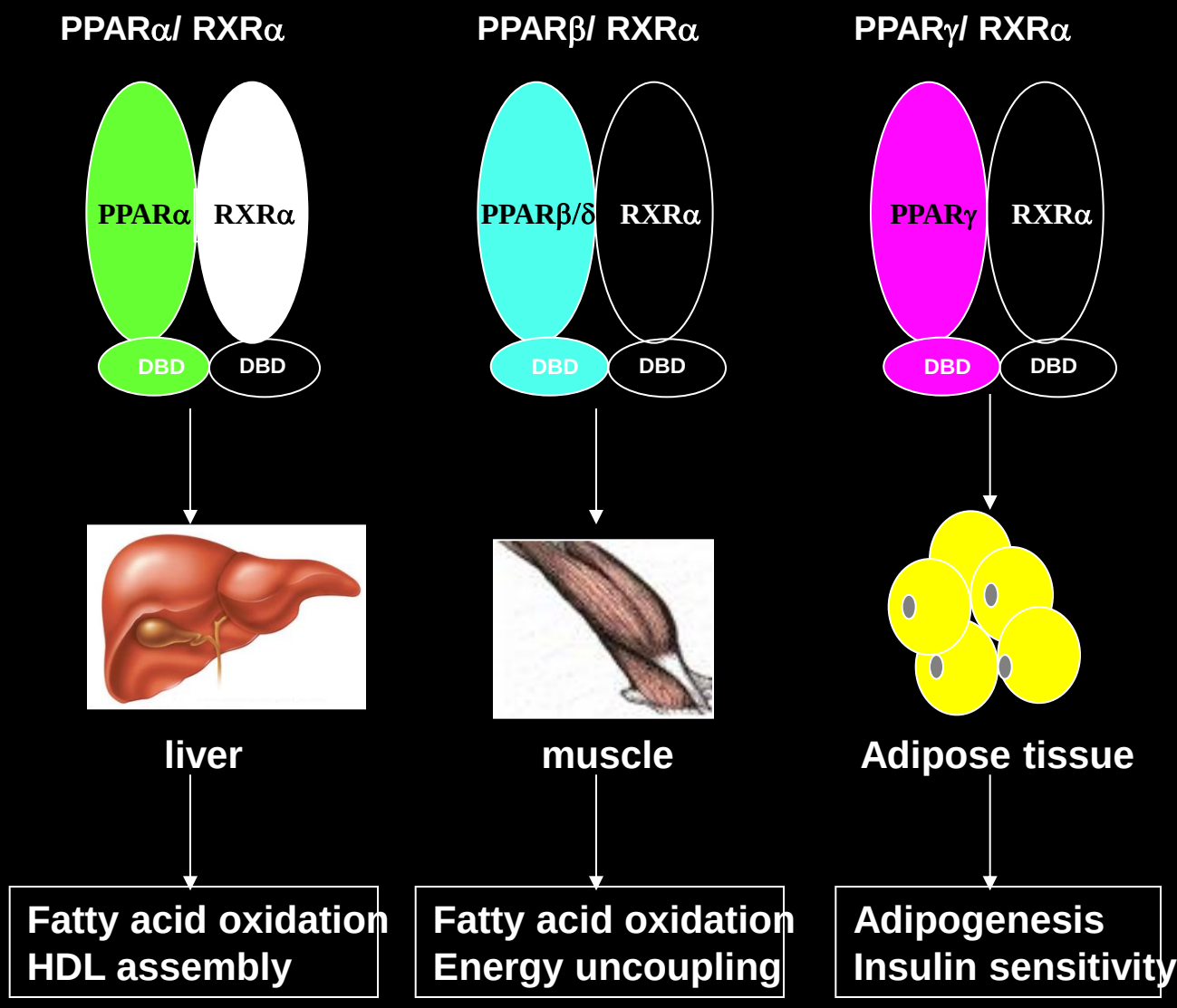
PPARs and diabetic nephropathy

代谢性核受体PPAR结构示意图
Functional domains of PPARs



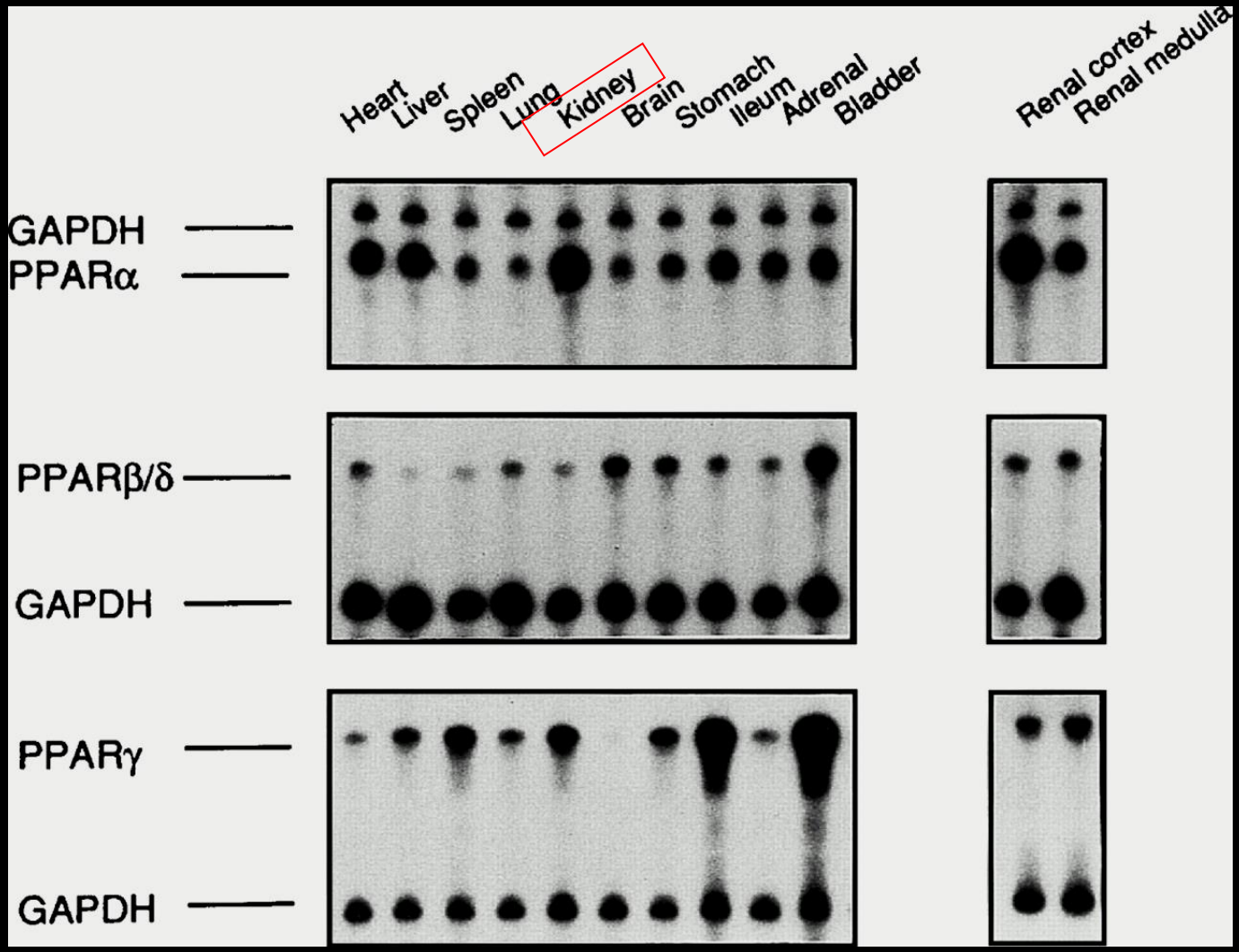


Metabolic regulation of PPARs



Ruan X, Zheng F, Guan Y. Am J Physiol Renal Physiol 2008

All PPAR isoforms are expressed in the kidney



Guan Y, et al Am J Physiol-Renal 1997

1. PPARα and diabetic nephropathy

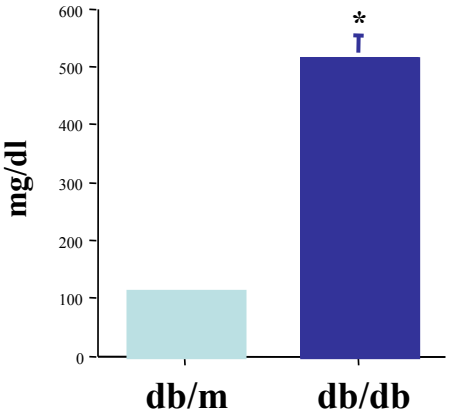
Murine model of type 2 diabetes：db/db mice

obesity

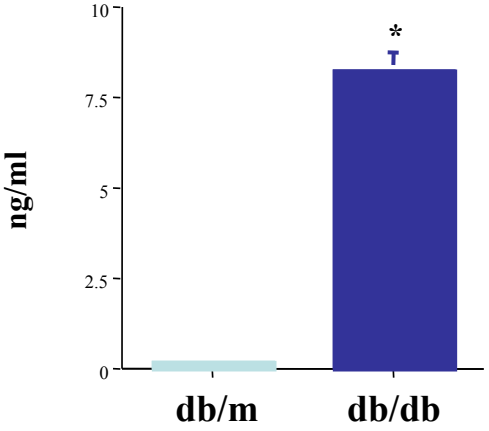
50.2 ± 4g　27.5 ± 0.4g

db/db mice　db / m

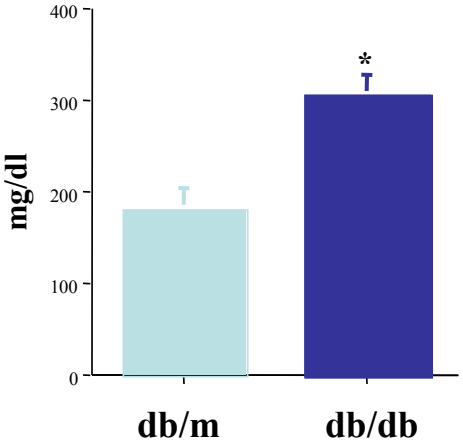
hyperglycemia



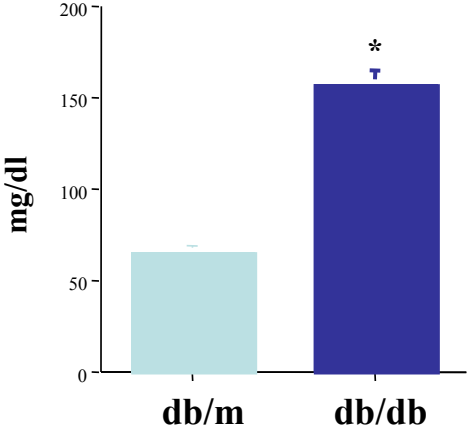
hyperinsulinemia



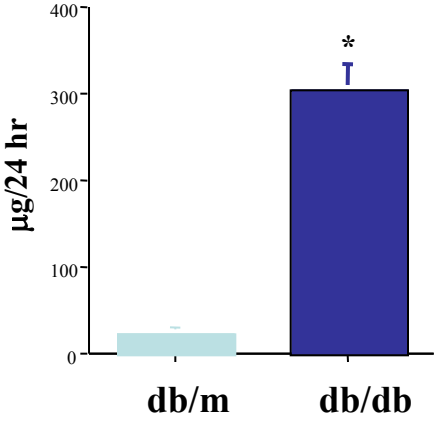
hypertriglyceridemia



hypercholesterolemia

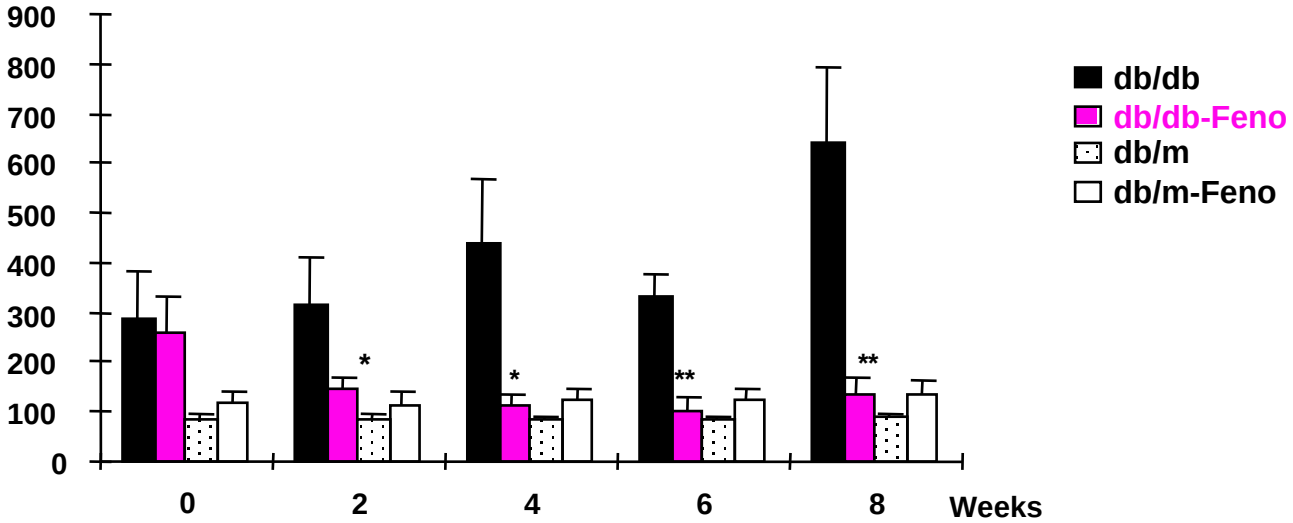


microalbuminuria

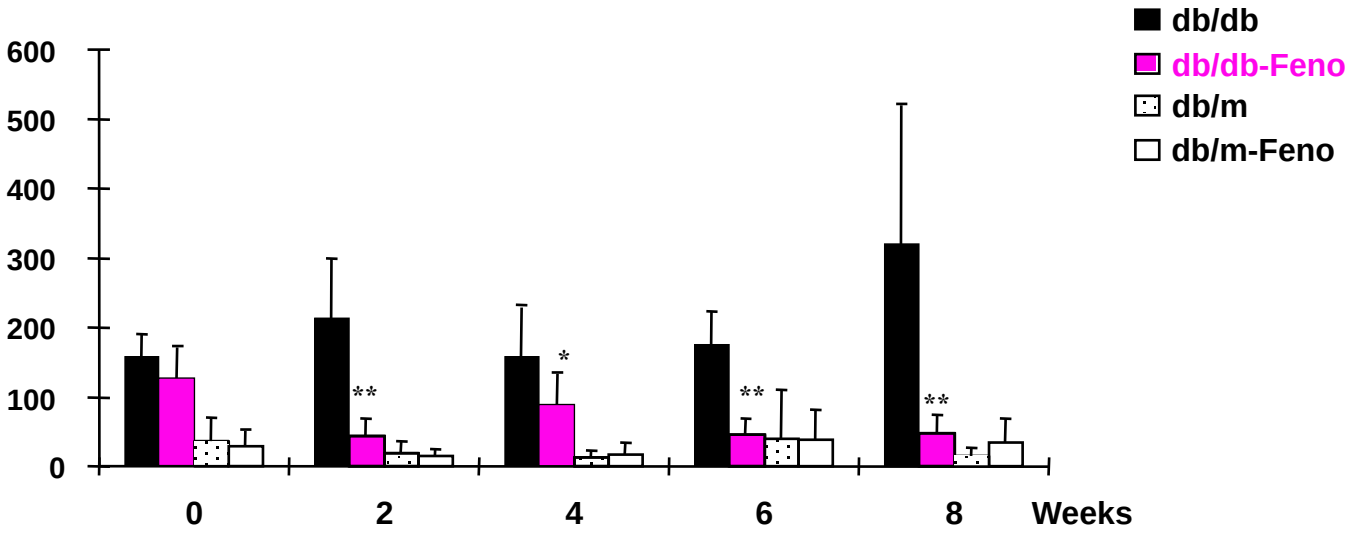


Effect of fenofibrate on fasting blood glucose and Ualb in db/db mice

Glucose (mg/dl)



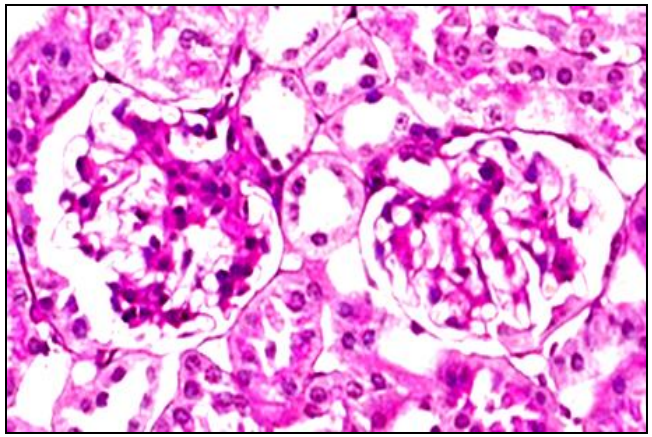
24 hrs urinary albumin (μg)



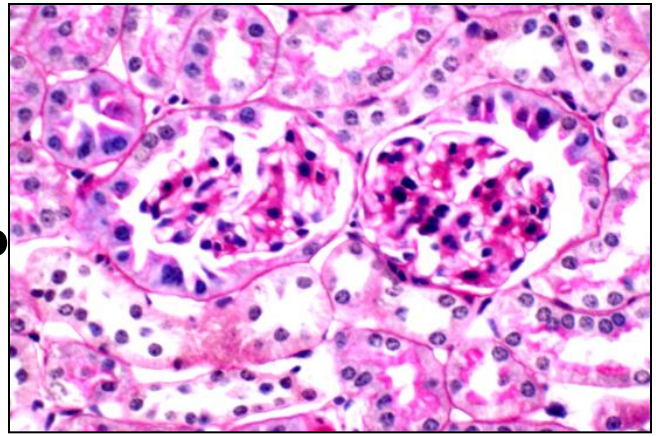
Park CW… Guan Y.
Kidney Int ., Diabetes 2006

Fenofibrate treatment attenuates glomerular fibrosis in db/db mice

db/db

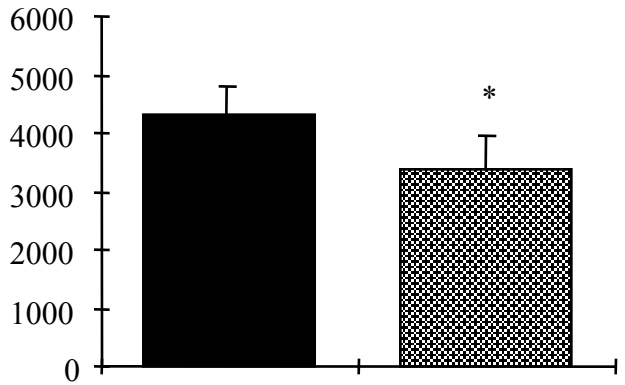


db/db-Feno

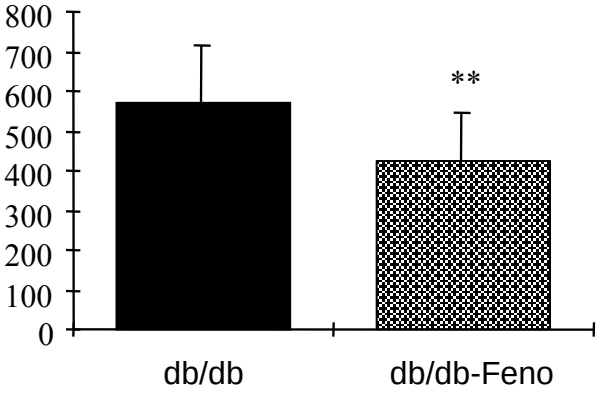


100 x

Glomerular surface area (μM²)



Mesangial surface area (μm2)



Summary

- **Fibrate PPARα activator attenuates albuminuria and renal fibrosis in db/db mice.**

Conclusions

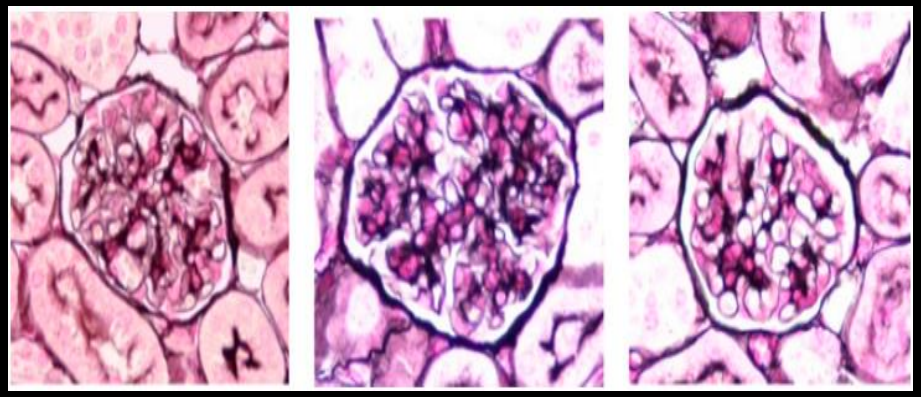
PPARα may represent a novel target for the treatment of diabetic nephropathy.

2. PPARβ与糖尿病肾病

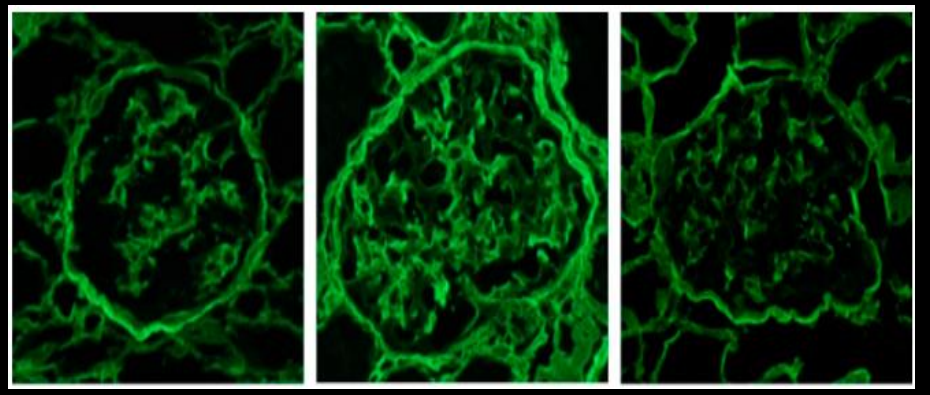
(PPARβ and DN)

PPARβ agonist GW0742 improves renal fibrosis in db/db mice

A

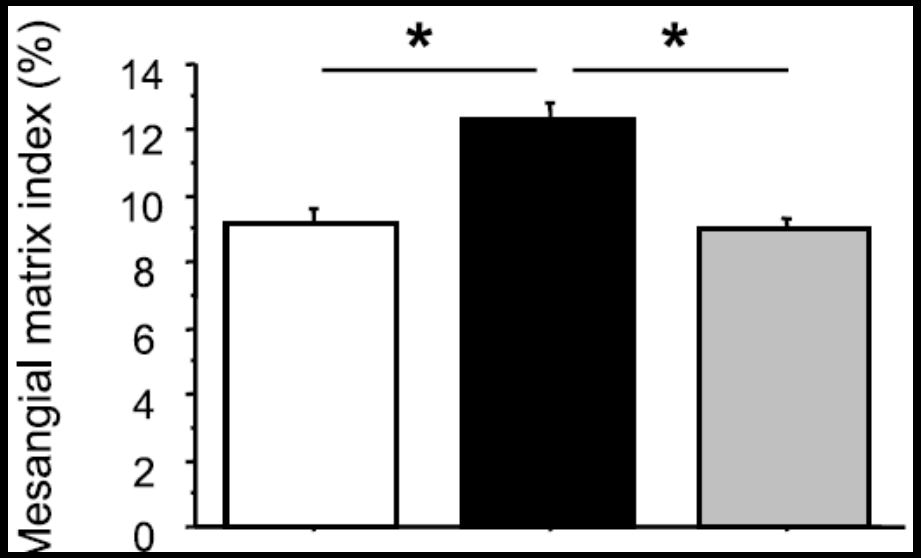


Control DM DM+GW0742

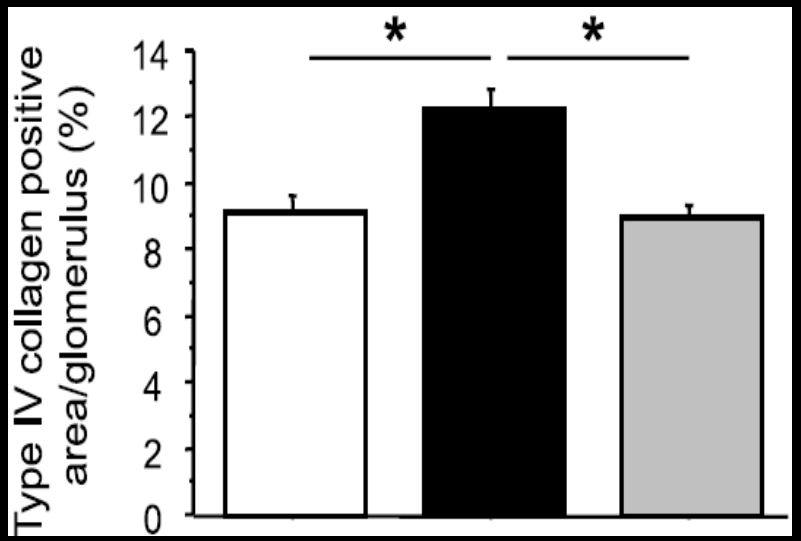


Control DM DM+GW0742

B



Control DM DM+GW0742



Control DM DM+GW0742

Matsushita Y, et al. Diabetes 2011

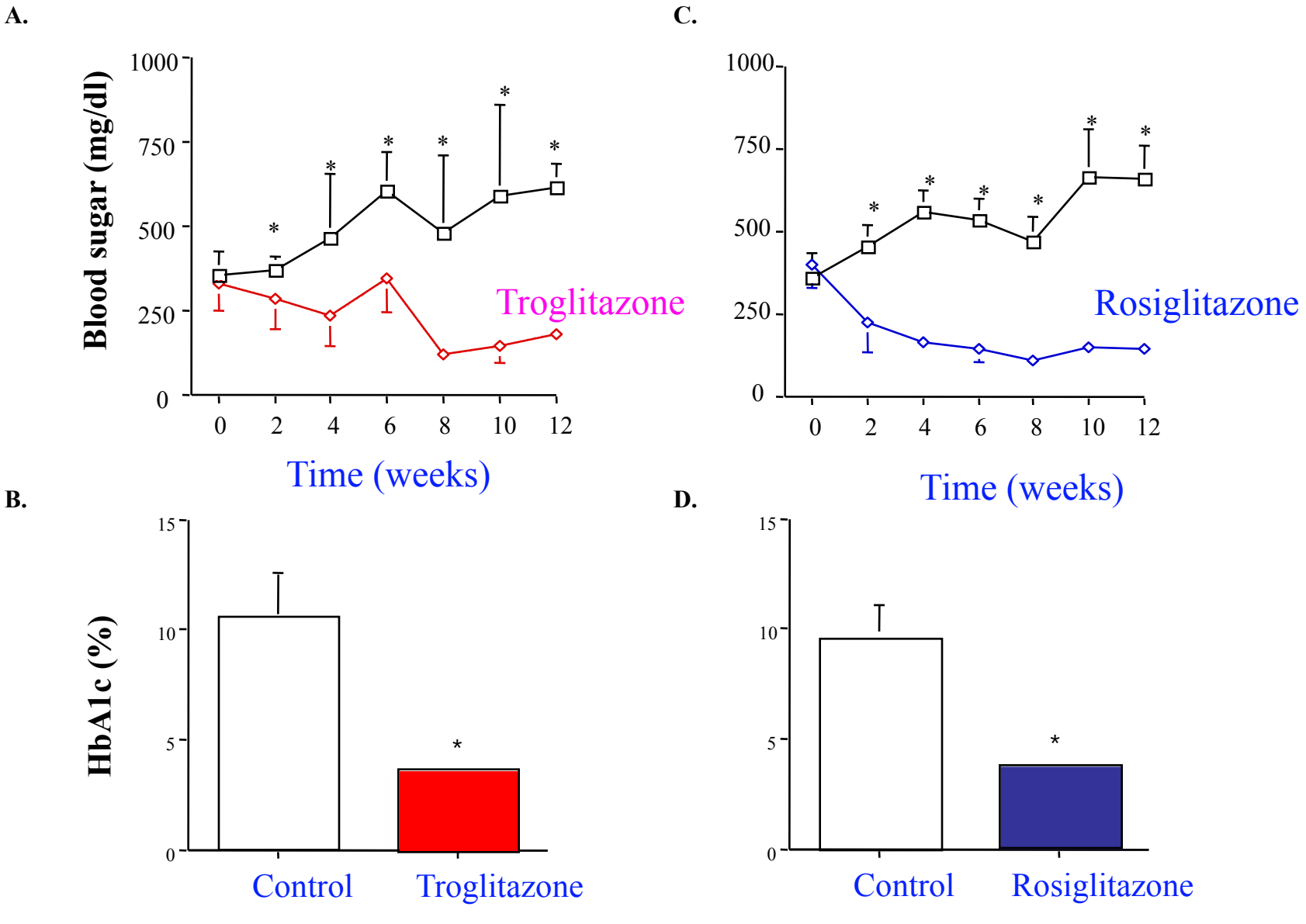
Summary and conclusion

PPARβ agonist GW0742 attenuates diabetes-associated renal fibrosis in db/db mice.

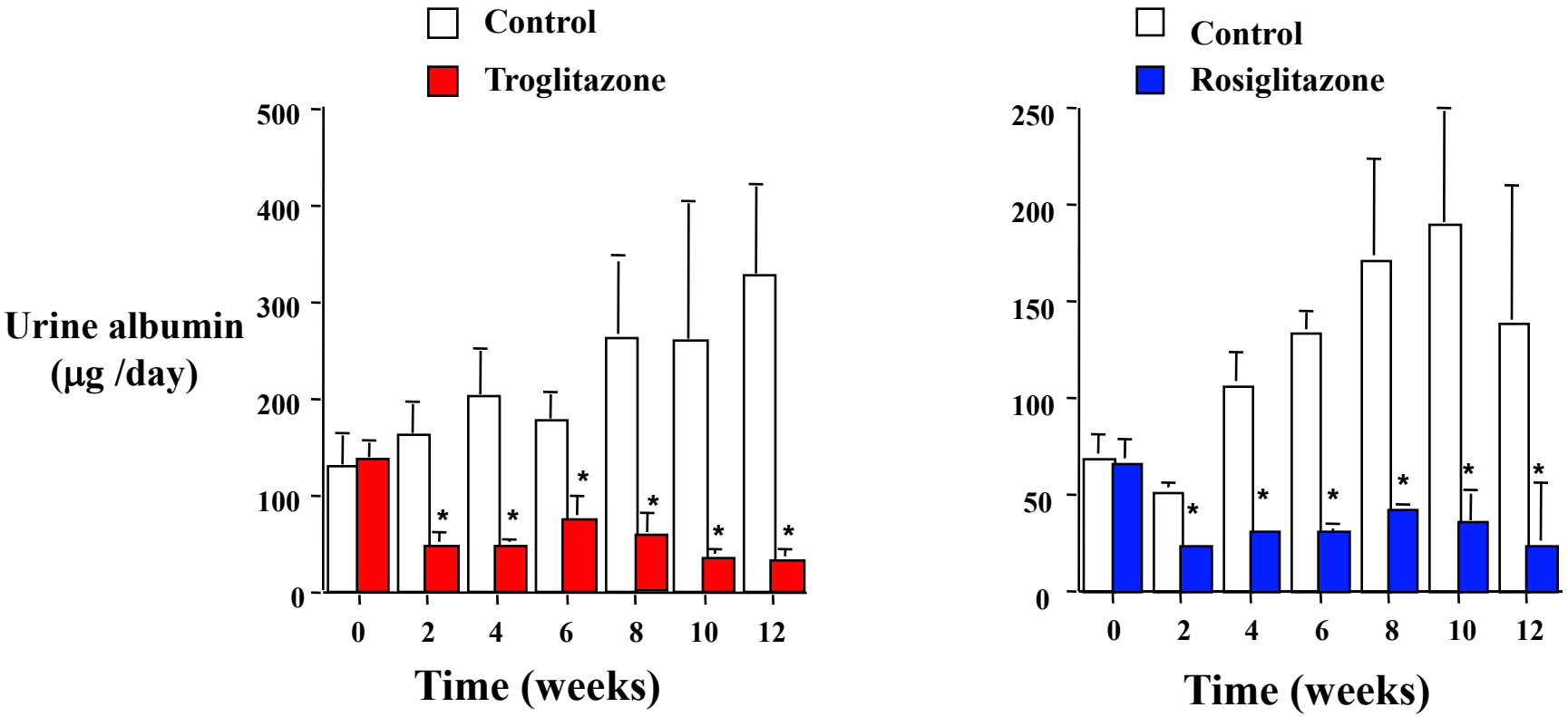
PPARβ agonist may act as a useful agent for the treatment of diabetic nephropathy.

3. PPARγ and diabetic nephropathy

TZD PPARγ ligands improve glycemic control in type 2 diabetic db/db mice

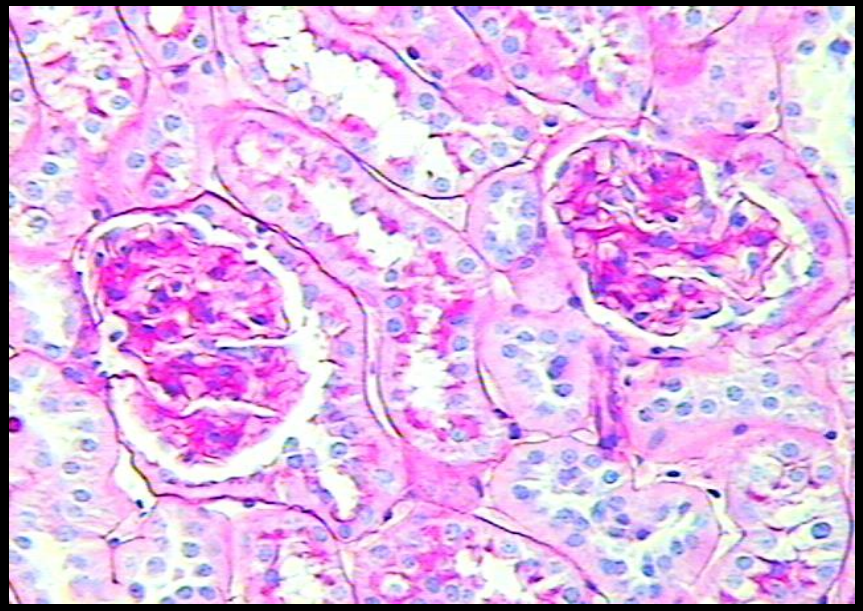


Effect of troglitazone and rosiglitazone on albuminuria in db/db mice

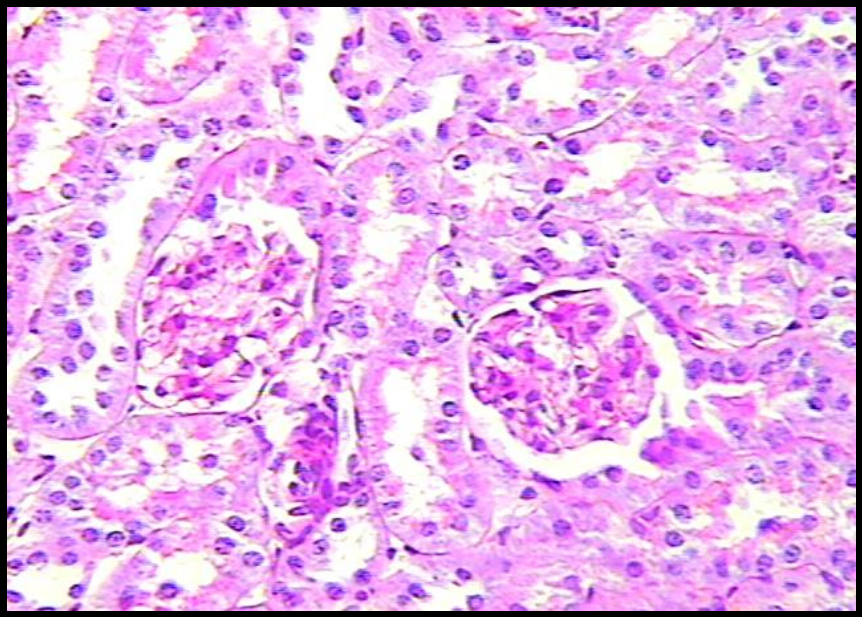


Male db/db mice (10 wks old) were treated with or without troglitazone or rosiglitazone for 12 wks.
*p<0.01, n=5.

Troglitazone ameliorates glomerular matrix expansion in db/db mice



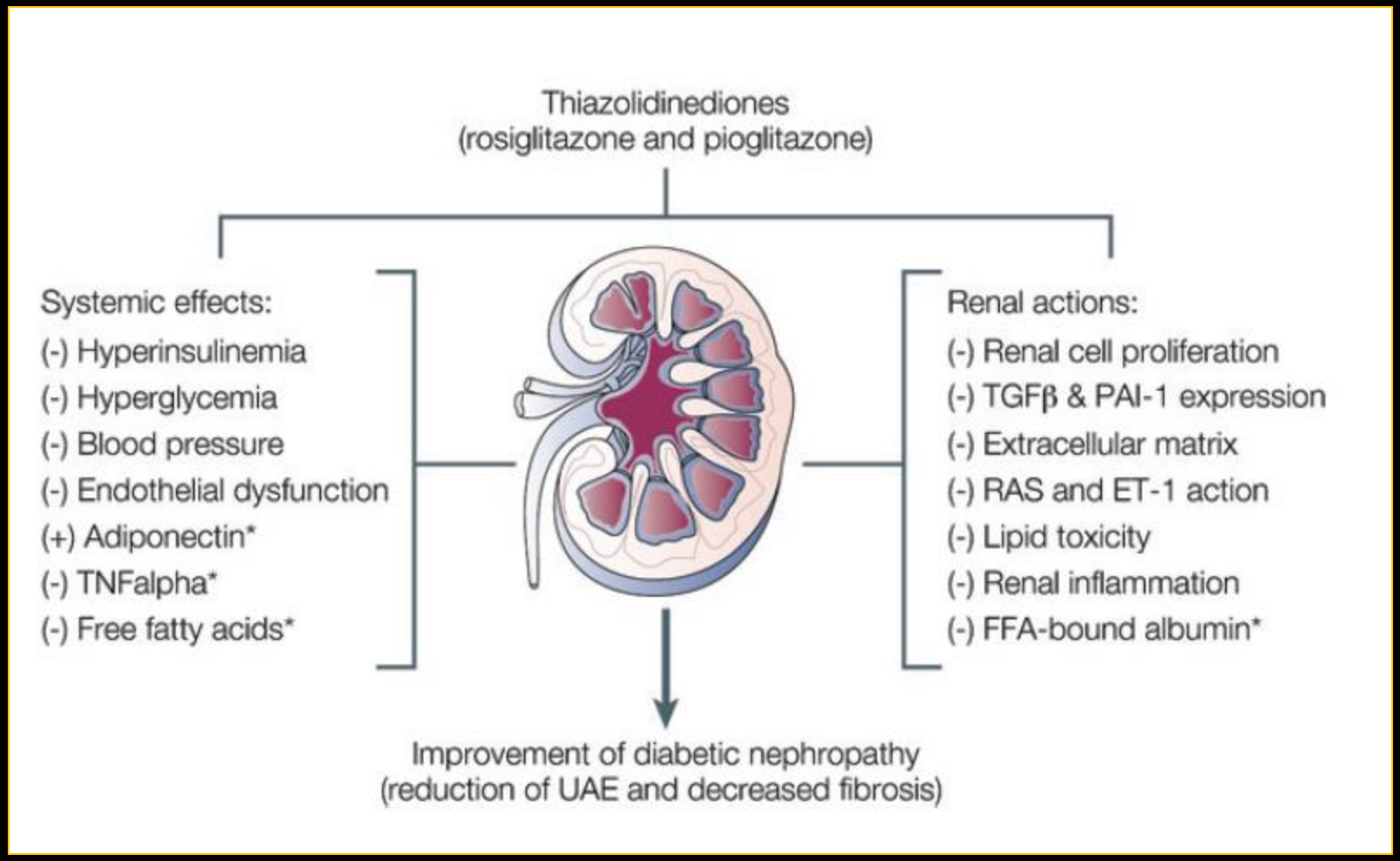
Control (PASx400)



Troglitazone treated (PASx400)

Male db/db mouse at age of10 weeks old was received troglitazone treatment or control vehicle (200 mg/kg/day) for 12 weeks. The kidneys were fixed and stained with PAS. Note that severe glomerulosclerosis and tubular hypertrophy were evident in control mouse,, while much less glomerulosclerosis and relative normal renal tubules were observed in troglitazone-treated mice.

Mechanisms involved in PPARγ-mediated improvement of chronic renal fibrosis



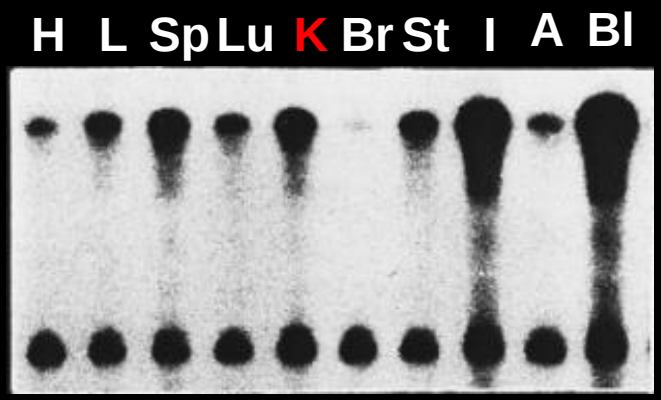
Yang J, et al. Curr Opin Nephrol Hypertens 2012
Zheng F, et al. Kidney Int 2007
Guan Y. Current Diabetes Report 2005

Molecular basis of TZD antidiabetic drug-induced edema

Up to 20% of patients receiving TZD PPARγ agonist treatment develop edema (water and sodium retention)

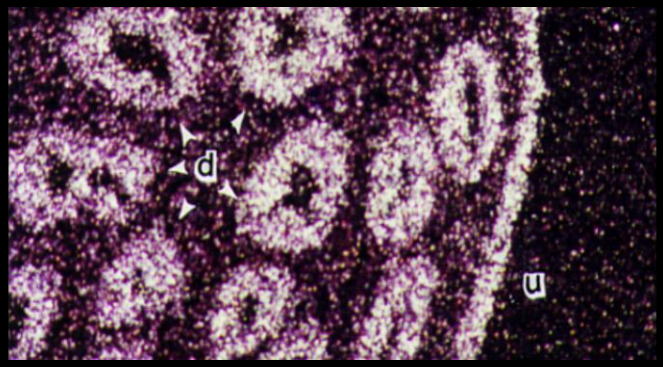
PPARγ is mainly localized in renal collecting duct.

A.



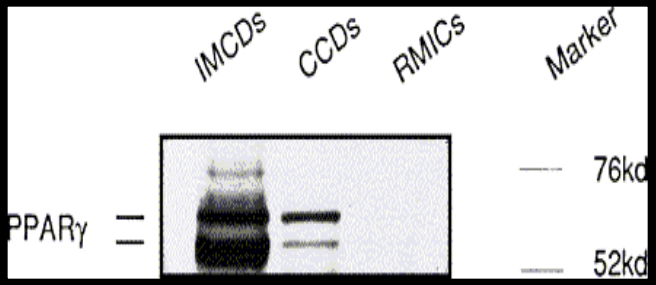
RNase protection

B.



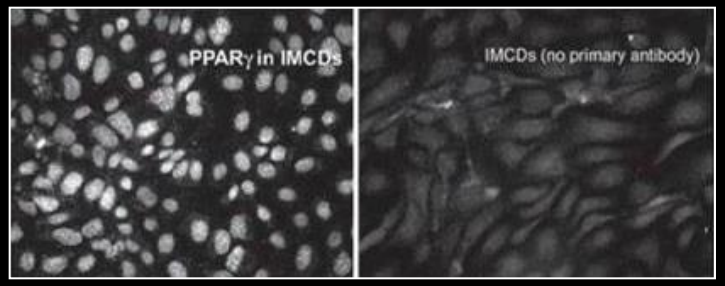
In situ hybridization

C.



Immunoblotting

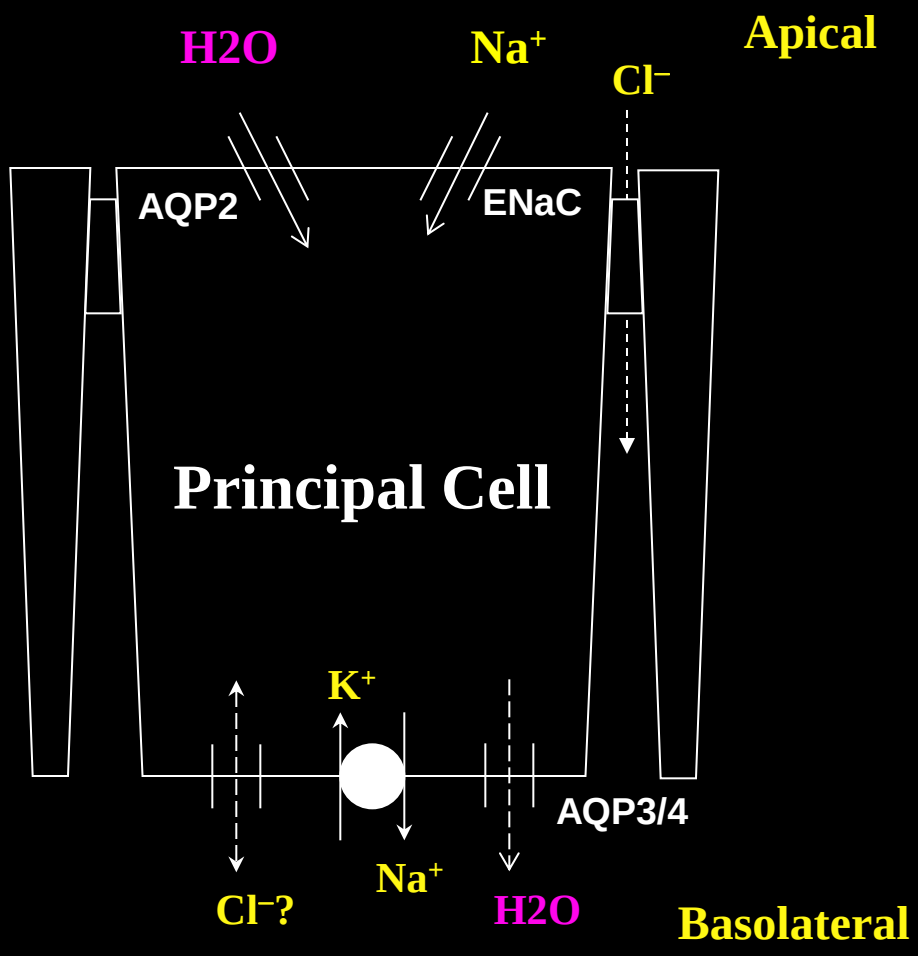
D.



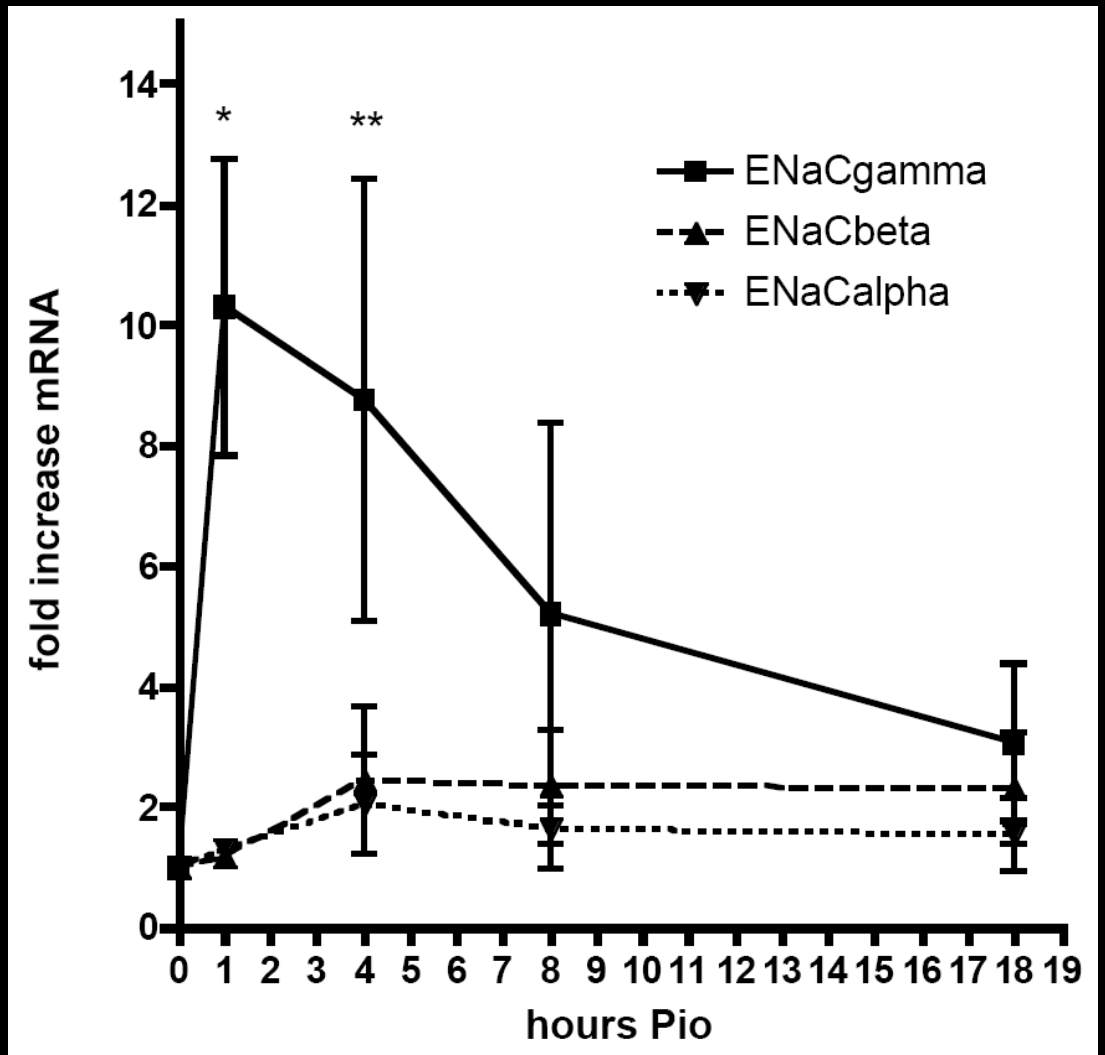
+1° Ab -1° Ab

Immunostaining

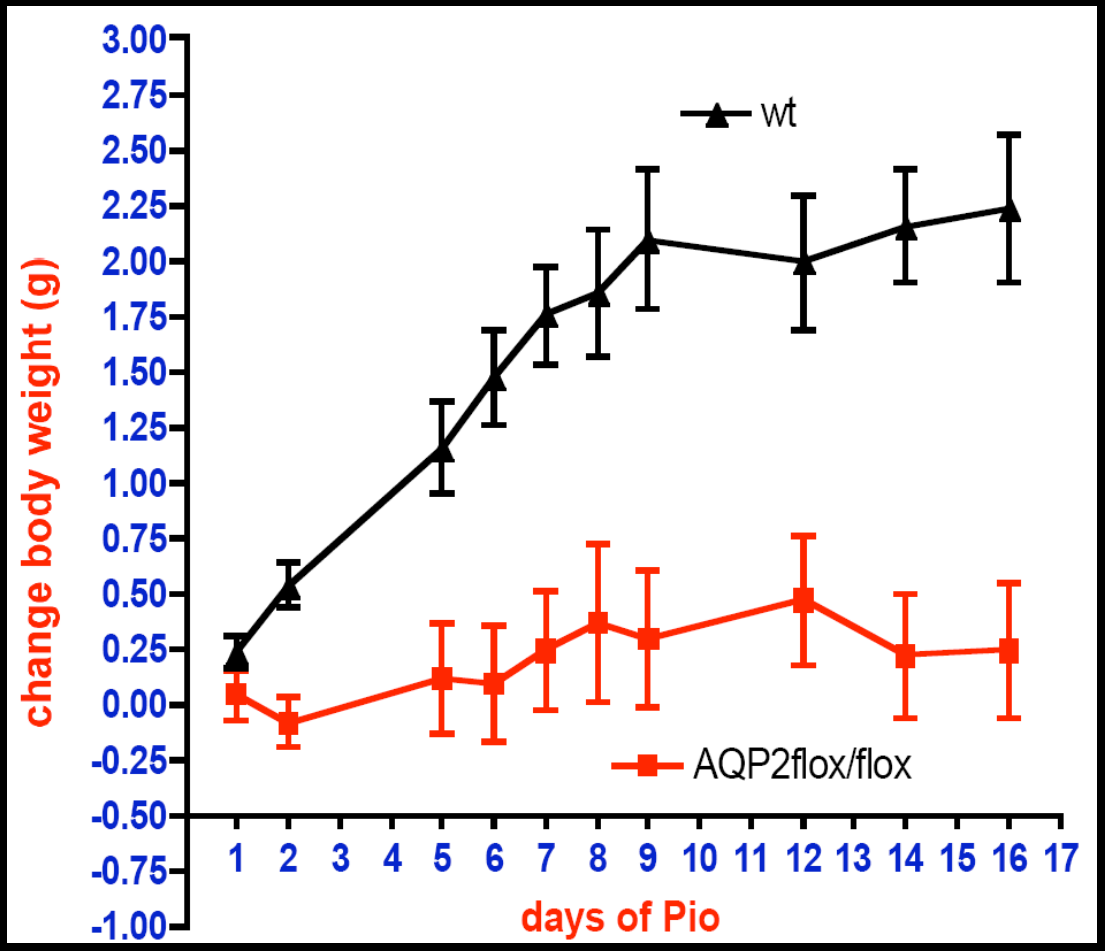
Hypothesis: Involvement of either Na^+,K^+, or Cl^- channel in sodium and water retention caused by TZD binding to PPARγ



Pioglitazone treatment increases ENaCγ Gene expression in cultured collecting ducts



Pioglitazone treatment increases body weight in wild-type, but not in AQP2flox/flox mice



Guan Y, et al. Nature Med 2005
Yang T, et al. PNAS 2005

Summary

- PPARγ is expressed in the kidney including in the glomerulus;
- TZDs improves diabetic nephropathy in db/db mice;
- Collecting duct PPARγ activation is the molecular basis for TZD-induced edema.

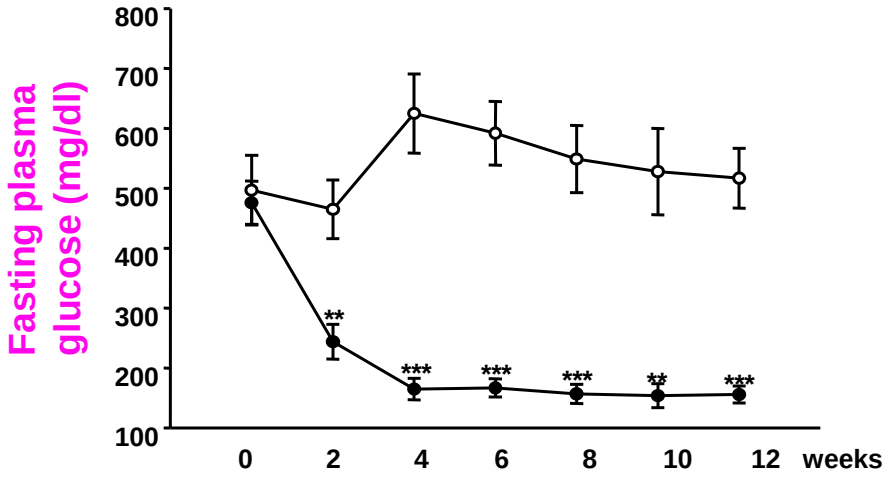
Conclusions

PPARγ may be a therapeutic target for treating diabetic nephropathy in type 2 diabetes. Its activation may result in water and sodium retention via increasing ENaC activity in collecting duct.

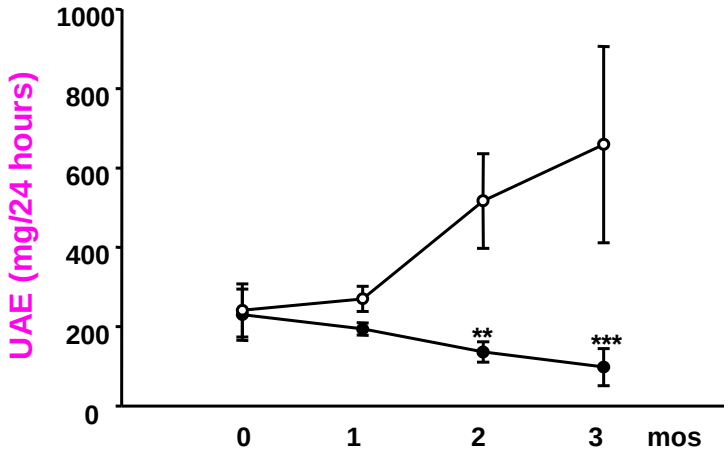
3. PPARα/γ dual activator and DN

PPARα/γ dual activator attenuates hyperglycemia and Ualb in db/db mice

A.

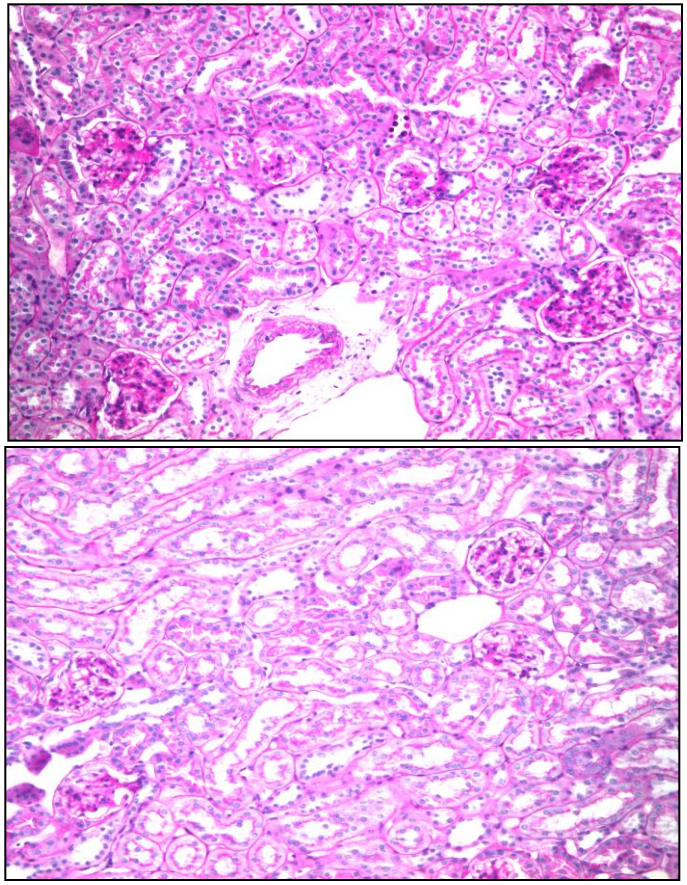


B.



Cha DR…Guan Y. Diabetes 2007

PPARα/γ dual activator ameliorates renal fibrosis

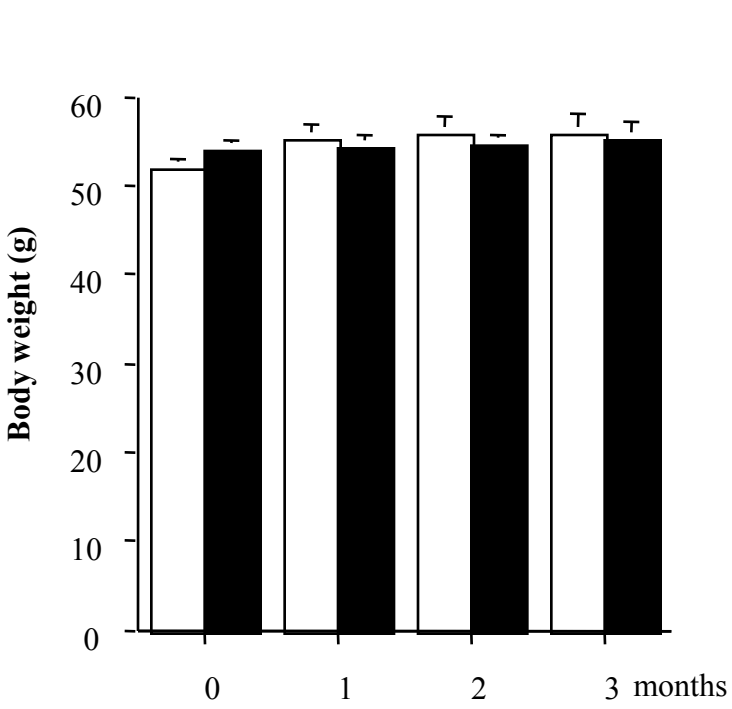


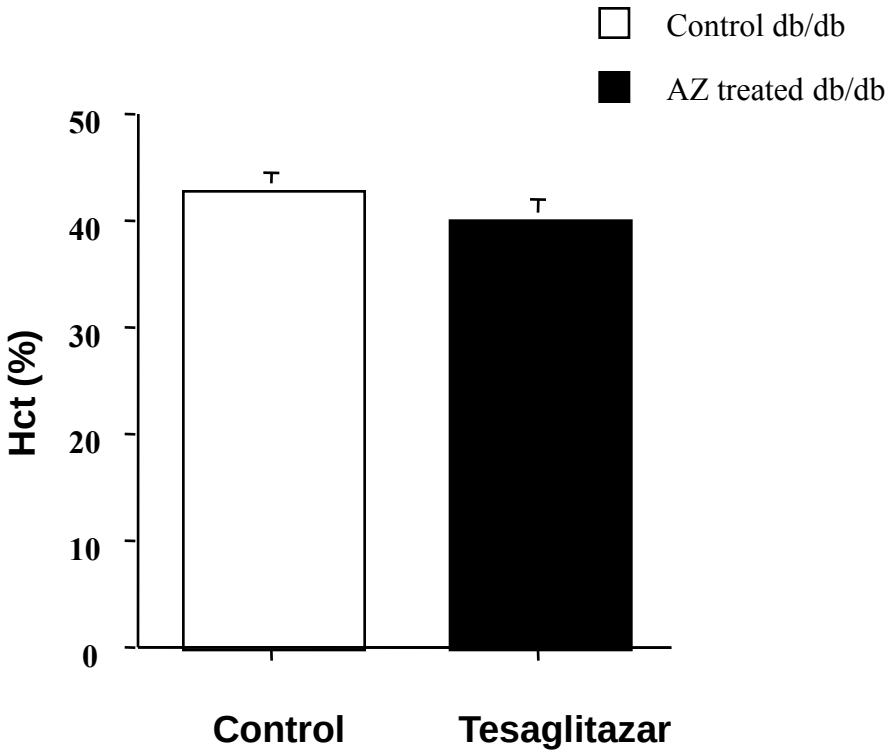
Control

AZ242

Cha DR…Guan Y. Diabetes 2007

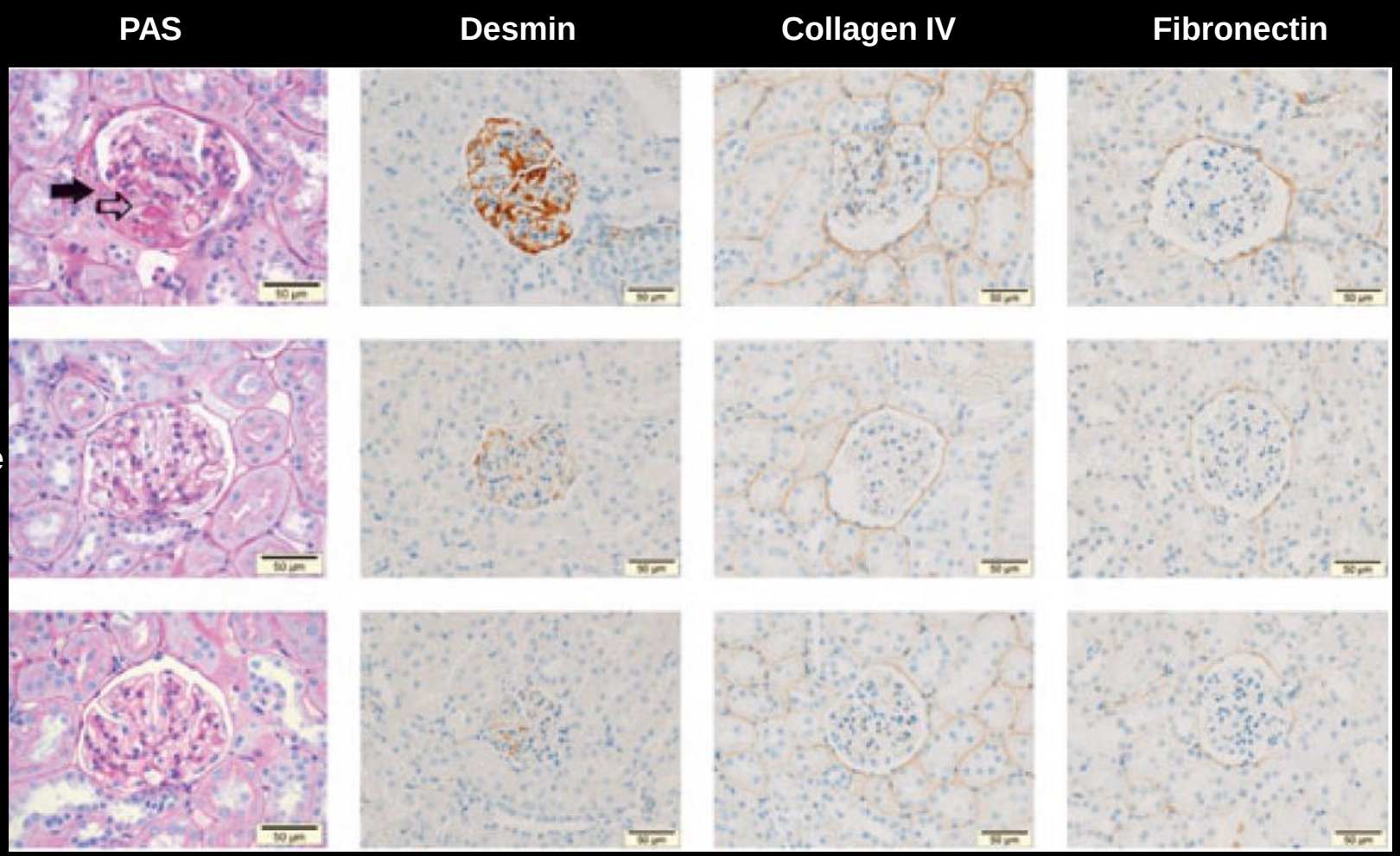
Little effect of PPARα/γ dual activator on hematocrit and body weight





Cha DR…Guan Y. Diabetes 2007

PPARα/γ dual agonist aleglitazar ameliorates renal fibrosis in Zucker diabetic rats



Benardeau A, et al. Diabetes Obes Metab 2012

Summary

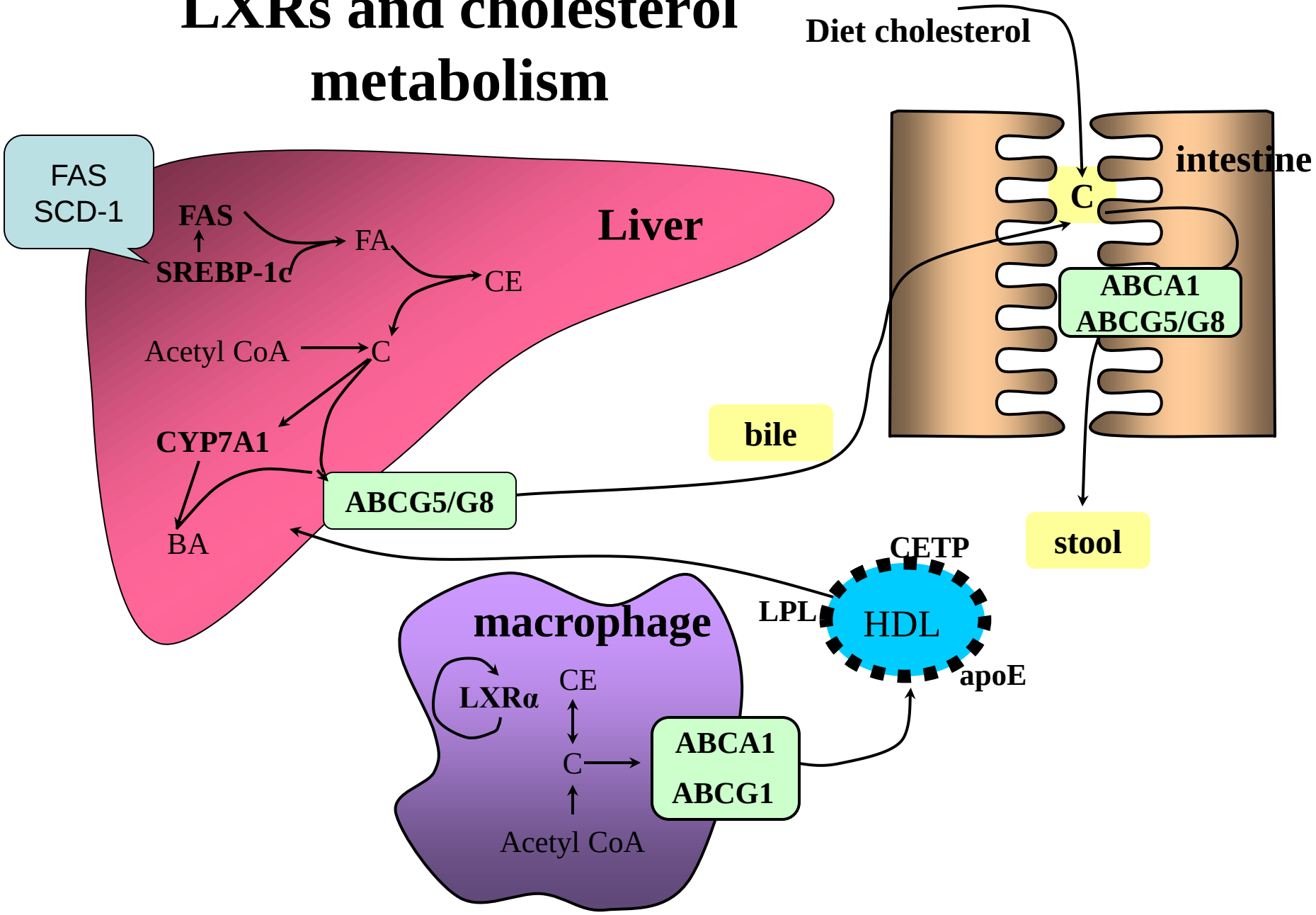
•PPARα/γ dual activator effectively improves diabetic nephropathy with little side-effect on water and sodium homeostasis.

Conclusions

PPARα/γ dual activator may act as a novel therapeutic agent for diabetic nephropathy.

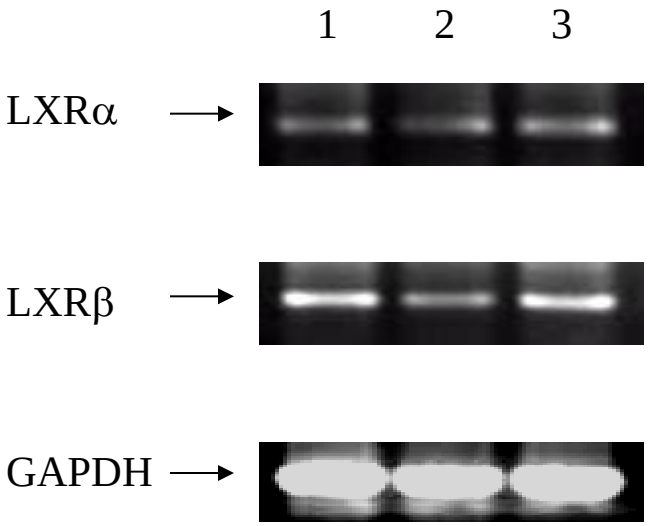
LXRs and diabetic nephropathy

LXRs and cholesterol metabolism

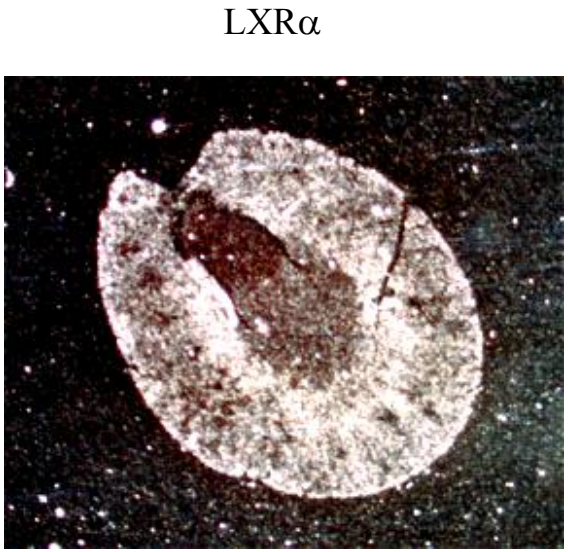


RT-PCR and in situ hybridization analysis of mouse LXRα in the kidney

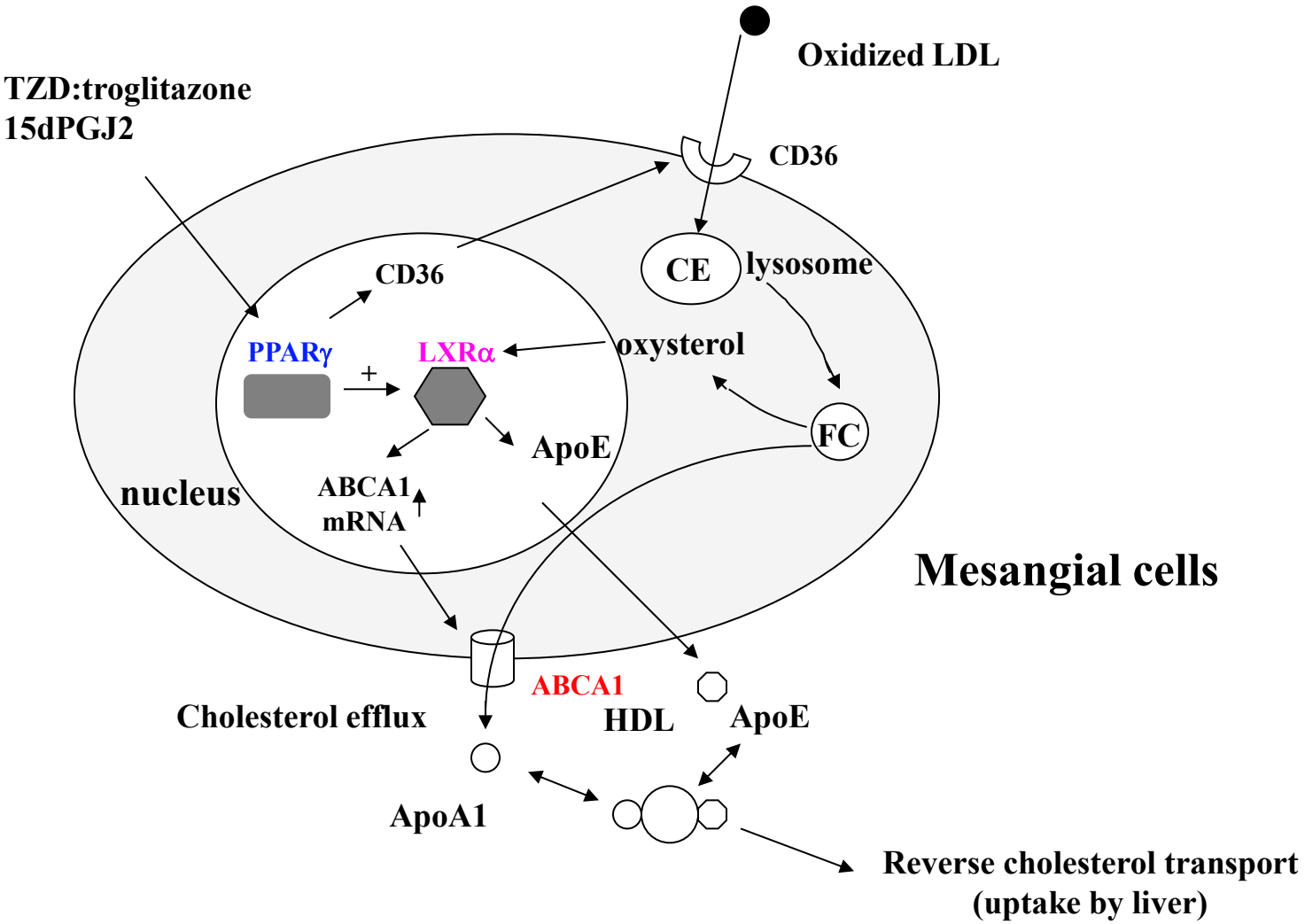
A. RT-PCR



B. In situ hybridization

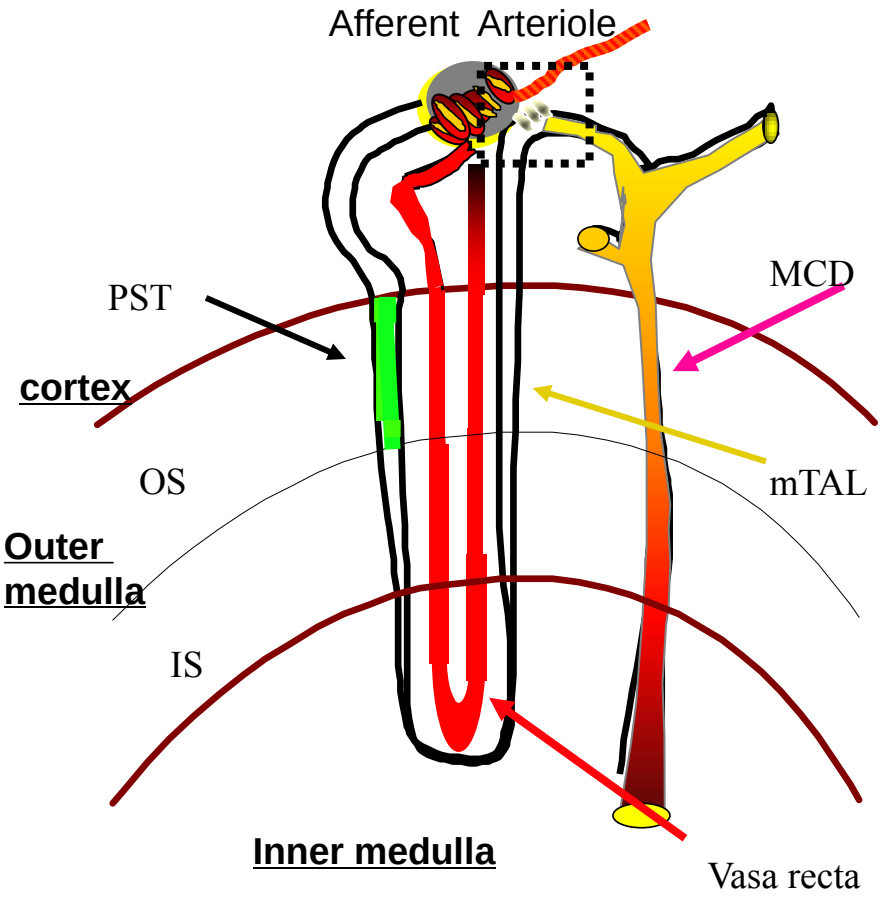


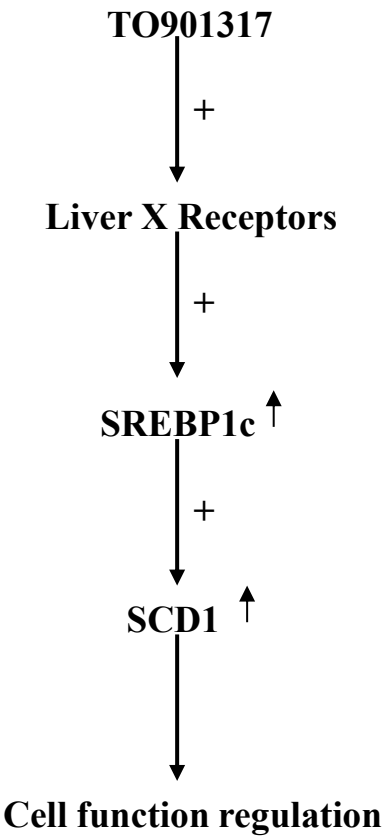
PPARγ enhances cholesterol efflux in glomerular mesangial cells via LXR-ABCA1 pathway



Wu J. …Guan Y AJP 2004

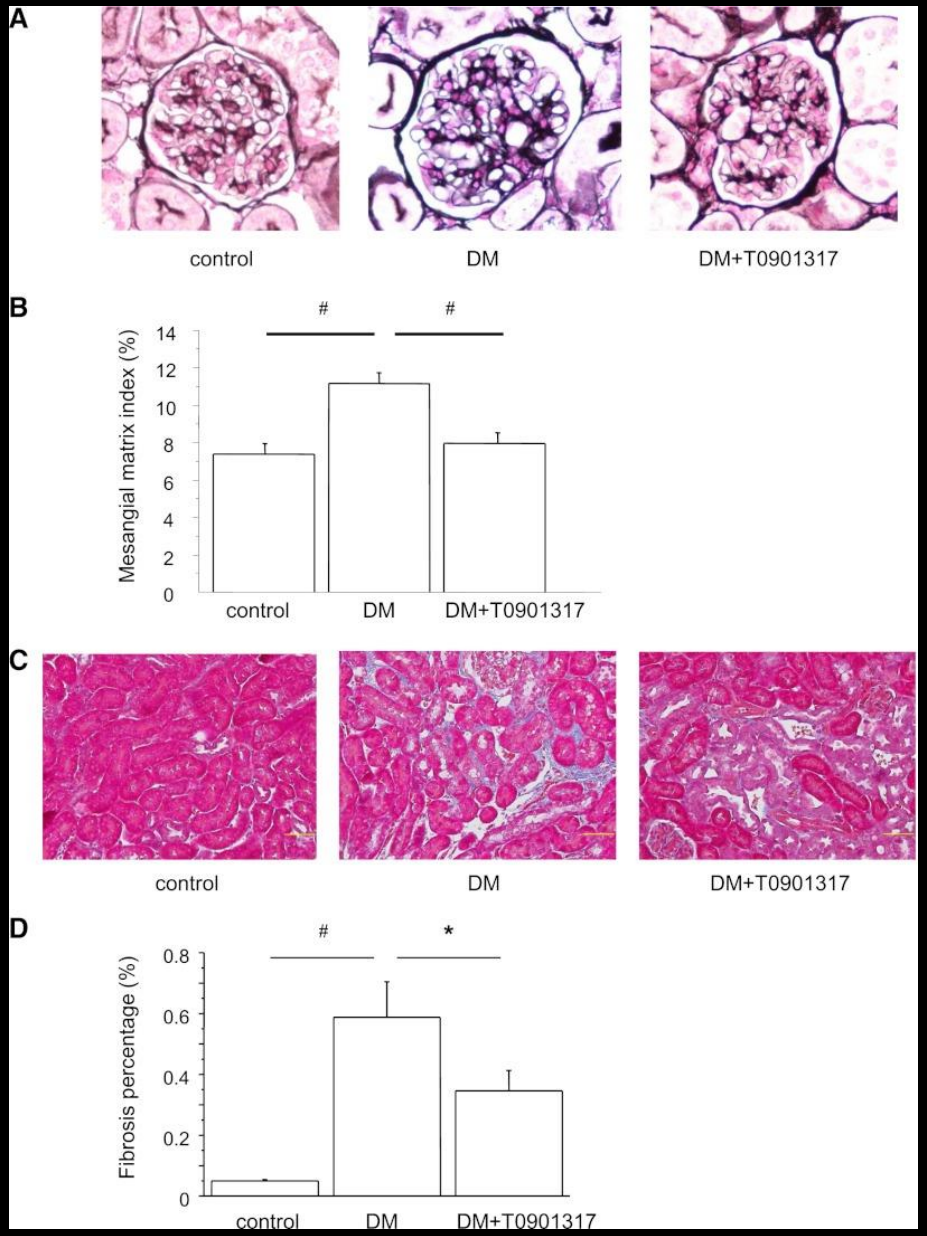
LXR increases SCD1 expression in a SREBP1c-dependent mamner in proximal straight tubules





Zhang Y, AJP-Renal 2006

LXR激动剂改善糖尿病肾病



Tachibana H. JASN 2012;
Kiss E. Am J Pathol 2013;
Patel M. Diabetelogia 2014

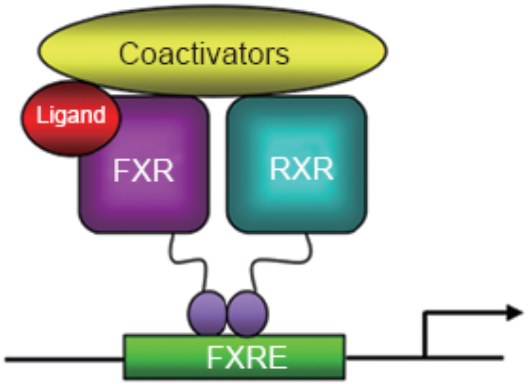
Summary & Conclusion

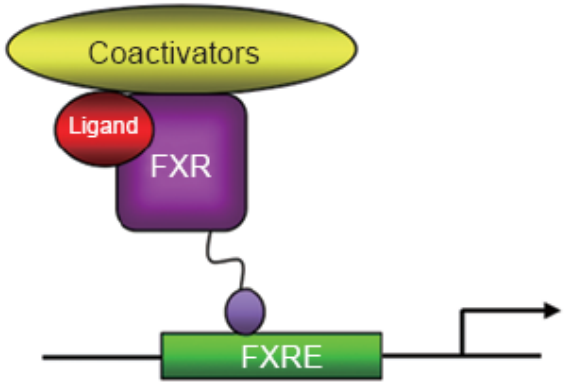
LXR may attenuate lipotoxicity in diabetic nephropathy in db/db mice.

LXR may represent a potential therapeutic target for the treatment of diabetic nephropathy.

3. FXRs and diabetic nephropathy

FXR plays an important role in regulating lipid and glucose metabolism





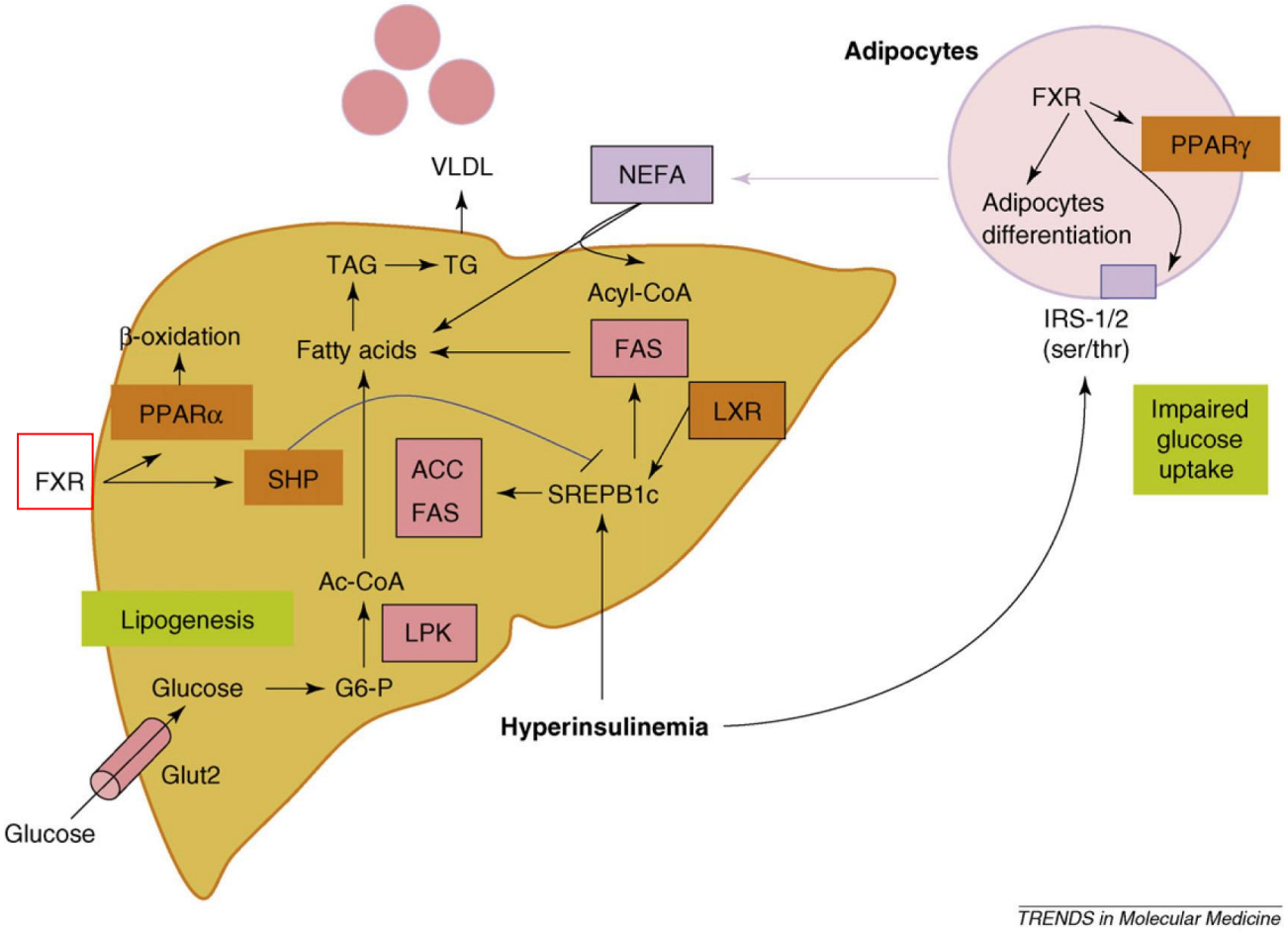
Bile acid metabolism:
Induced:
BACS
BAT
BSEP
Hepatic insig-2
IBABP
rMRP2
OATP8
hOSTα/hOSTβ
SHP
STD
Suppressed:
ASBT
CYP7A1
CYP8B1

Lipoprotein metabolism:
Induced:
Apolipoprotein C-II
Apolipoprotein E
Human complement C3
MDR3
PLTP
SDC1
VLDLR
Suppressed:
ApoA-1
Hepatic lipase
Apo CIII

Glucose metabolism:
PEPCK
G6Pase

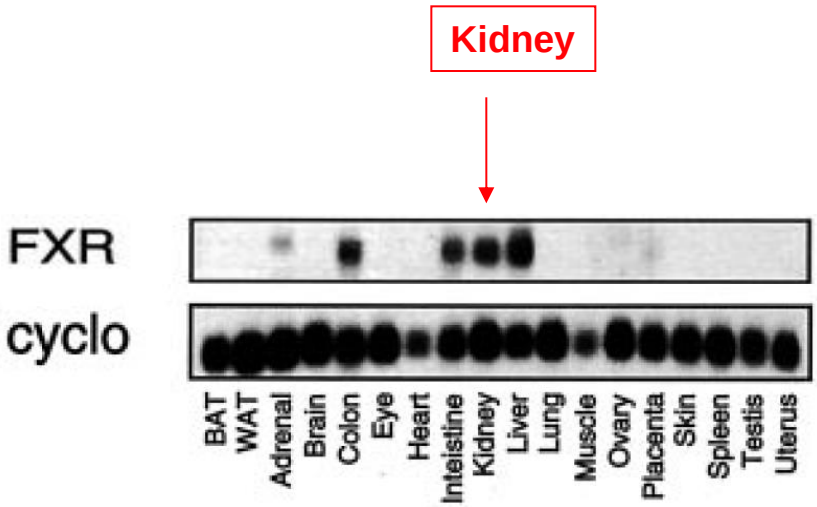
Cell Res. 2008 Nov;18(11):1087-95.

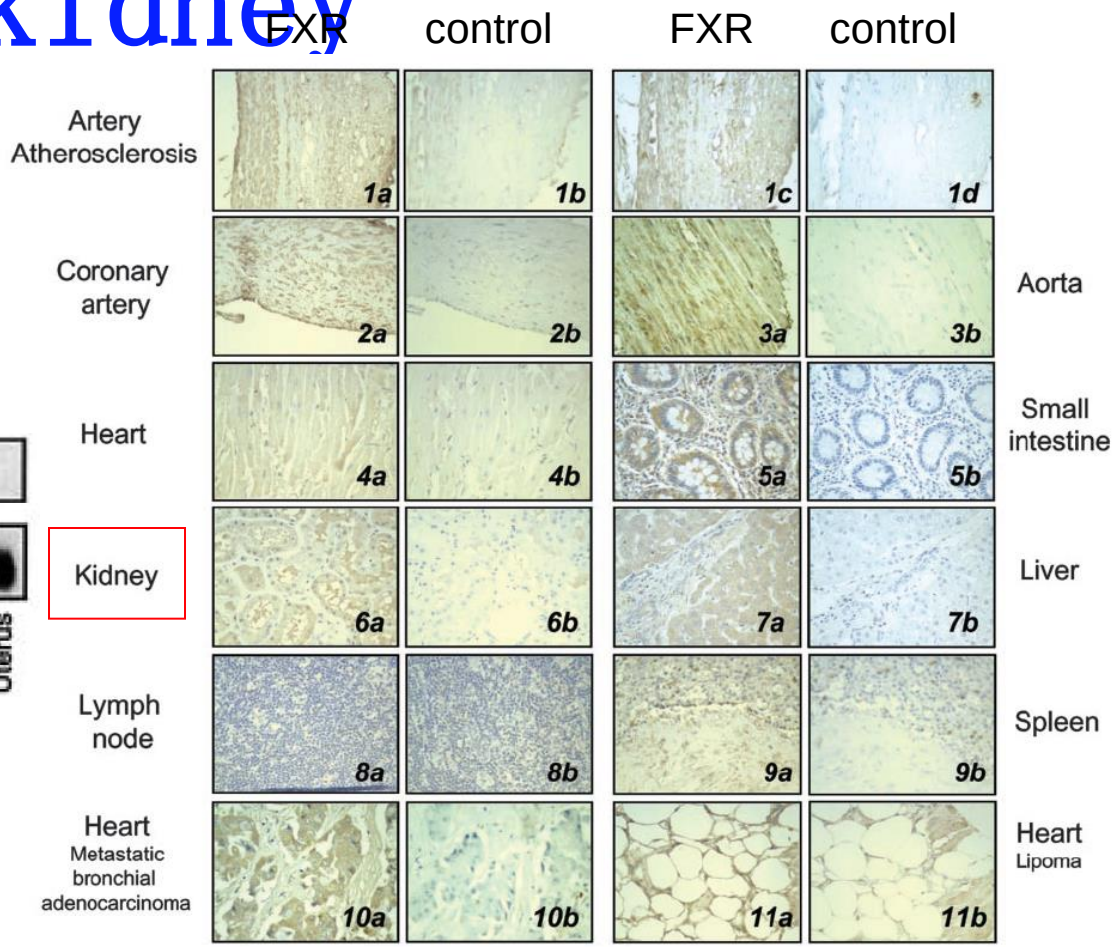
FXR is critical in cholesterol metabolism



Trends Pharmacol Sci. 2007 May;28(5):236-43.

FXR is highly expressed in the kidney

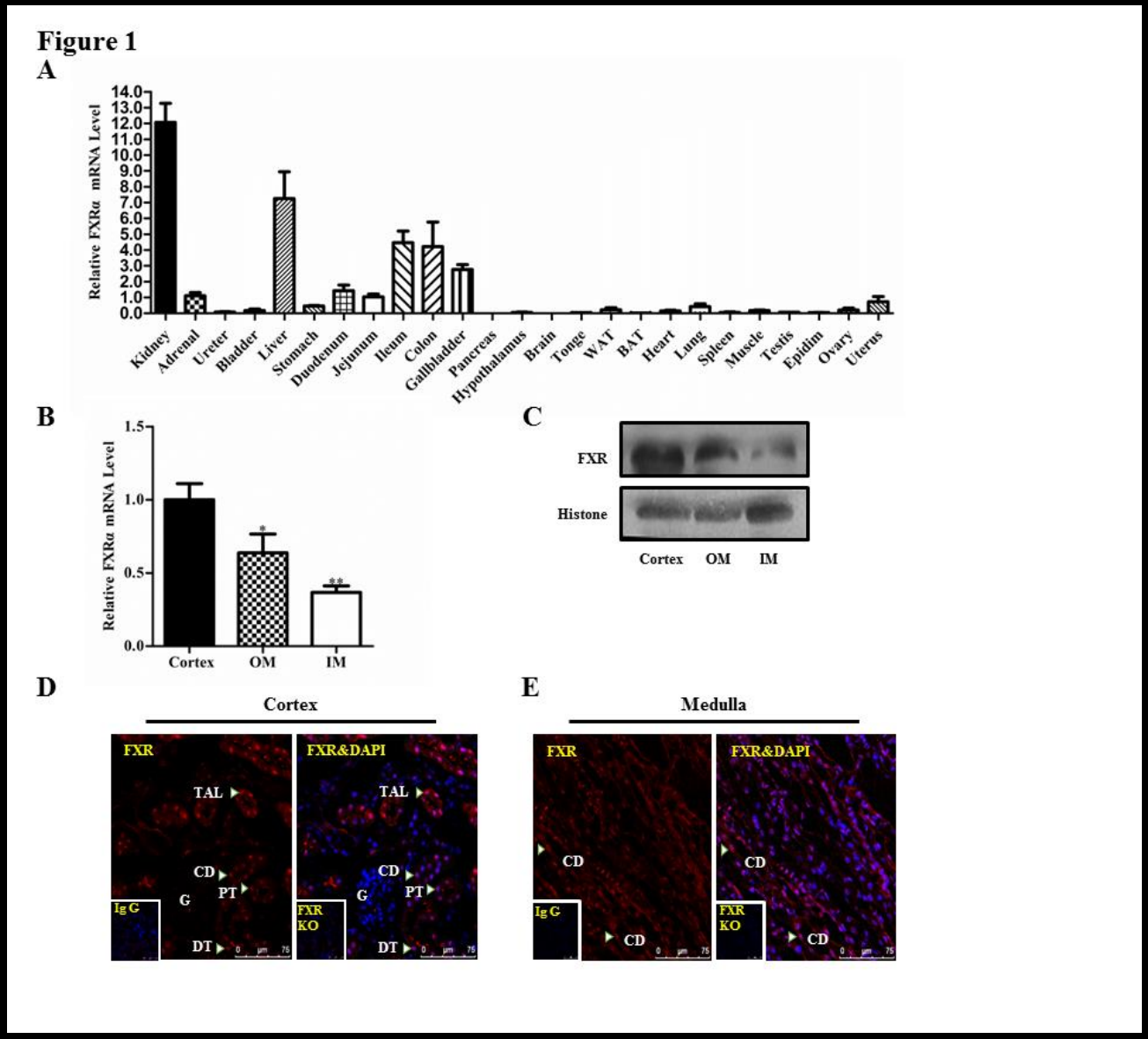




JBC 2001, 276: 37735-37738

PNAS 2004, 101: 3668-3673

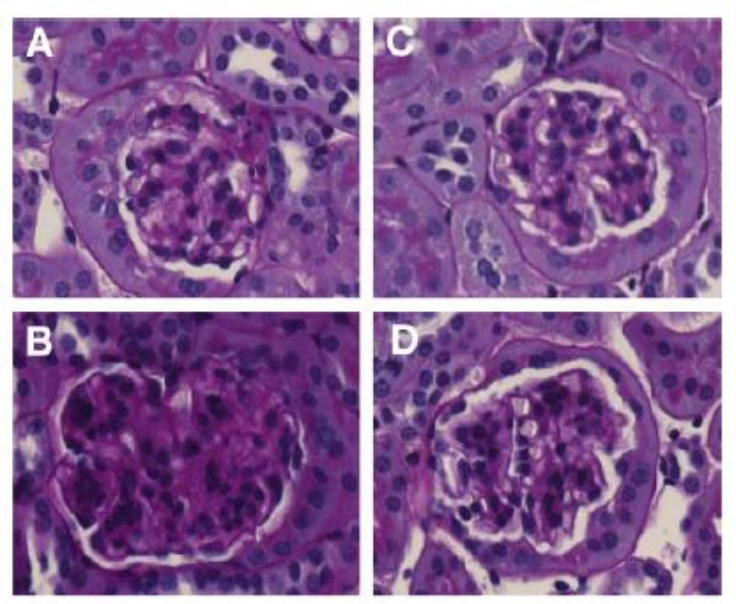
FXR广泛表达在肾脏组织中



Zhang XY, et al. PNAS 2014

FXR activator exerts renoprotective effects in type 2 diabetic mice

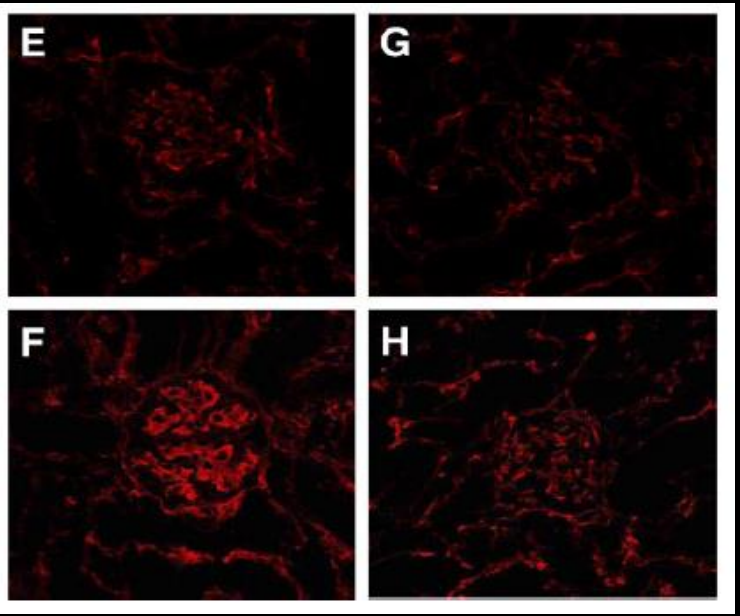
db/m db/m+cholic acid



db/db db/db+cholic acid

PAS Staining

db/m db/m+cholic acid

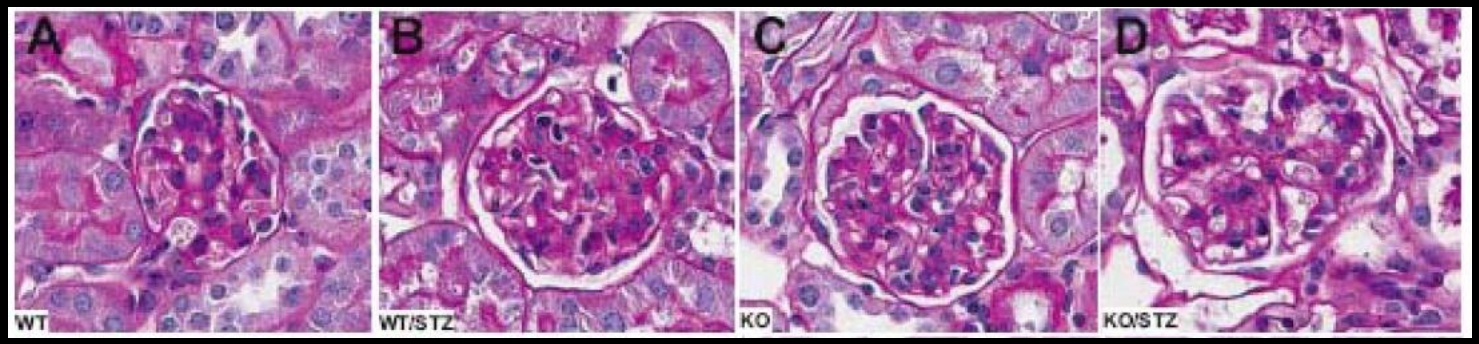


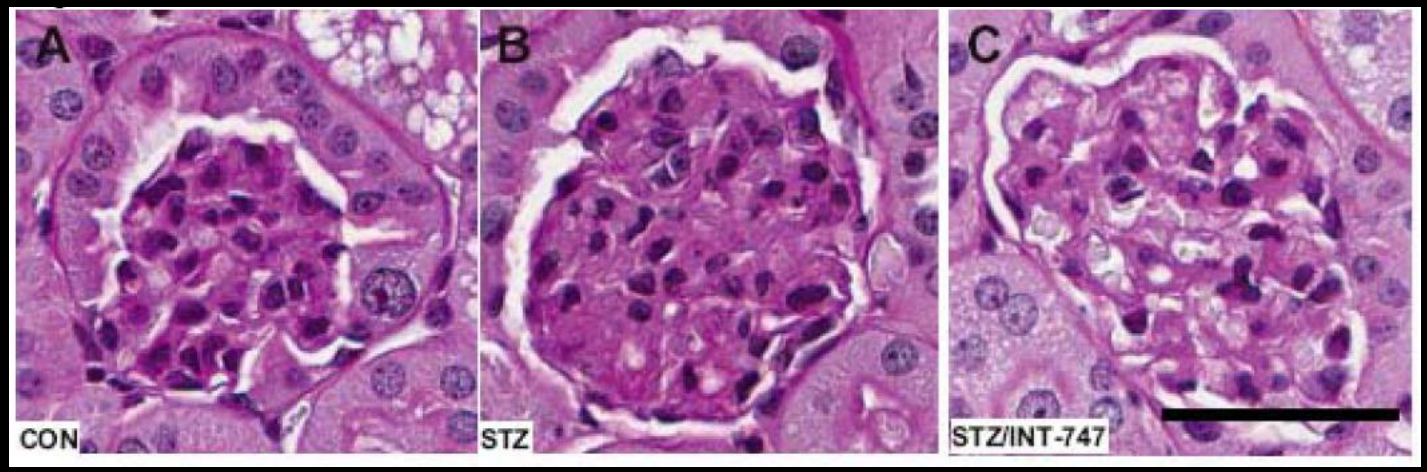
db/db db/db+cholic acid

Fibronectin

Jiang T, et al. Diabetes. 2007 Oct;56(10):2485-93

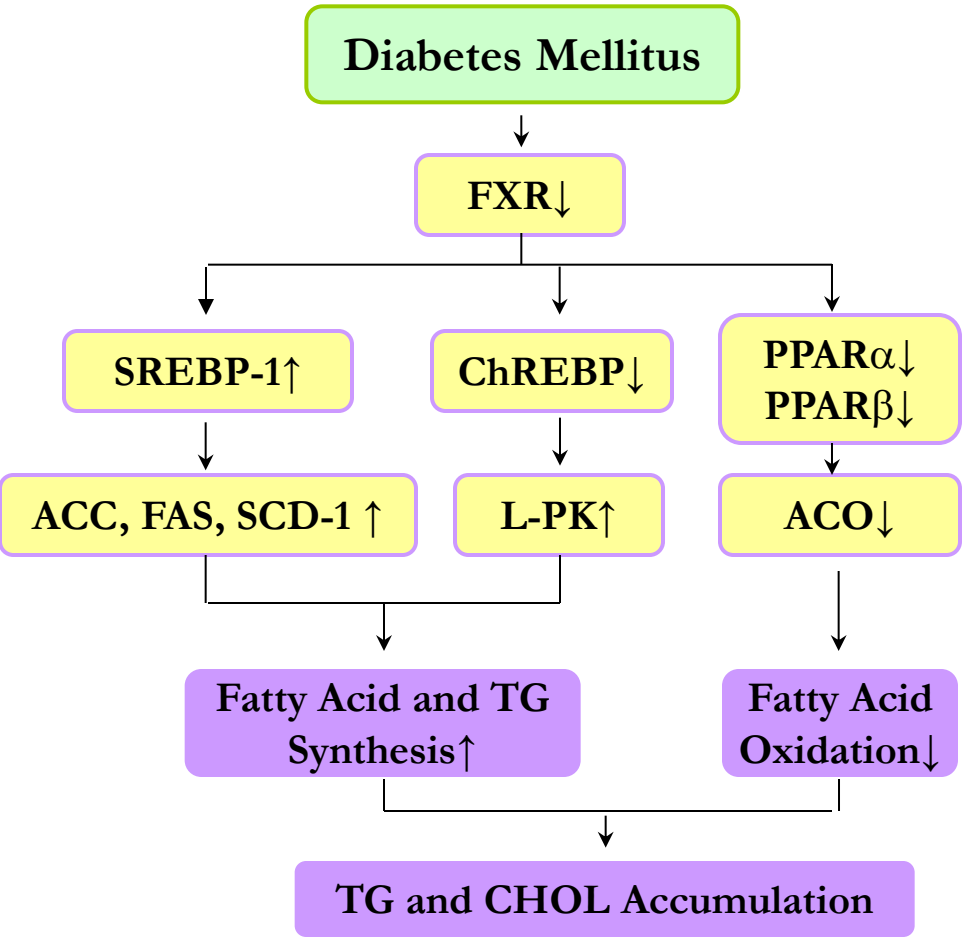
FXR activation improves, while FXR inactivation worsens diabetic nephropathy in STZ-induced tyep 1 diabetic mice



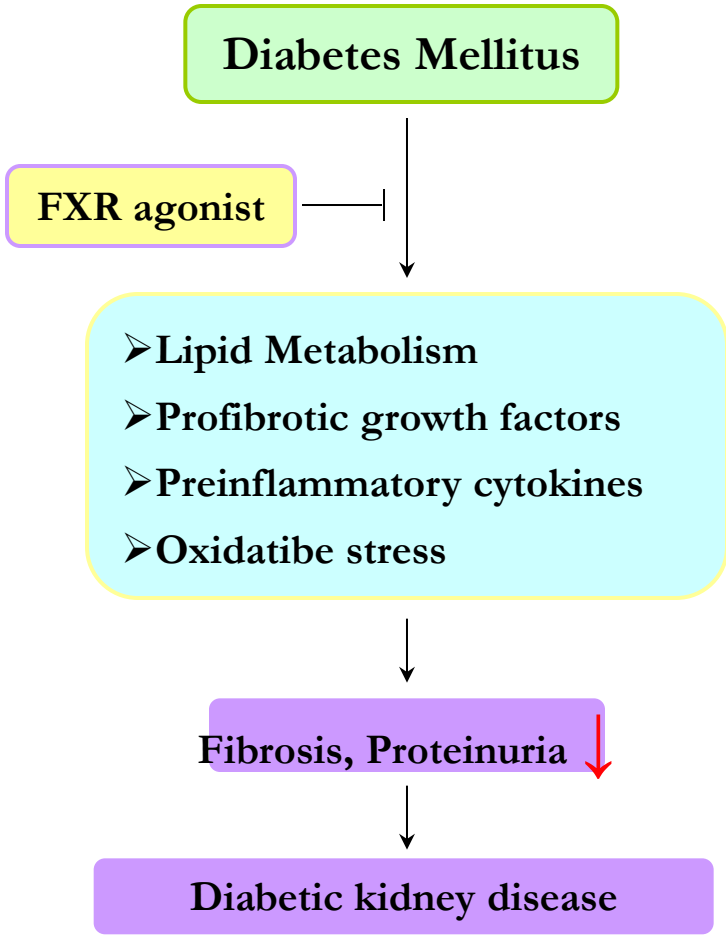


Wang X, et al. Diabetes 2010 ;59(11):2916-27

Molecular mechanisms involved in renoprotective effects of FXR



Diabetes. 2006 Sep;55(9):2502-9.
Diabetes. 2005 Aug;54(8):2328-35.



Diabetes. 2007 Oct;56(10):2485-93.

Farnesoid X receptor (FXR) gene deficiency impairs urine concentration in mice

Xiaoyan Zhang[a,b,1], Shizheng Huang[a,1], Min Gao[a], Jia Liu[a], Xiao Jia[a], Qifei Han[a], Senfeng Zheng[a], Yifei Miao[c], Shuo Li[a], Haoyu Weng[a], Xuan Xia[a], Shengnan Du[a], Wanfu Wu[c], Jan-Åke Gustafsson[c,d,2], and Youfei Guan[a,b,2]

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Contributed by Jan-Åke Gustafsson, December 23, 2013 (sent for review November 15, 2013)

Zhang X, et al. Proc Natl Acad Sci U S A. 2014 Feb 11;111(6):2277-82

Summary & Conclusion

FXR is highly expressed in the kidney；

FXR activation attenuates lipotoxicity and diabetic nephropathy in both type 1 and type 2 diabetes.

FXR is a promising therapeutic target for diabetic nephropathy.

Acknowledgments

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Cha Dae, MD

3. University of Miami (Division of Nephrology)

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生理学研究所
肾脏病研究中心
心血管研究中心
代谢疾病研究中心
脑与神经疾病研究中心

医学研究的前沿
学科发展的平台
人才培育的基地
体制创新的特区

大连医科大学糖尿病中心

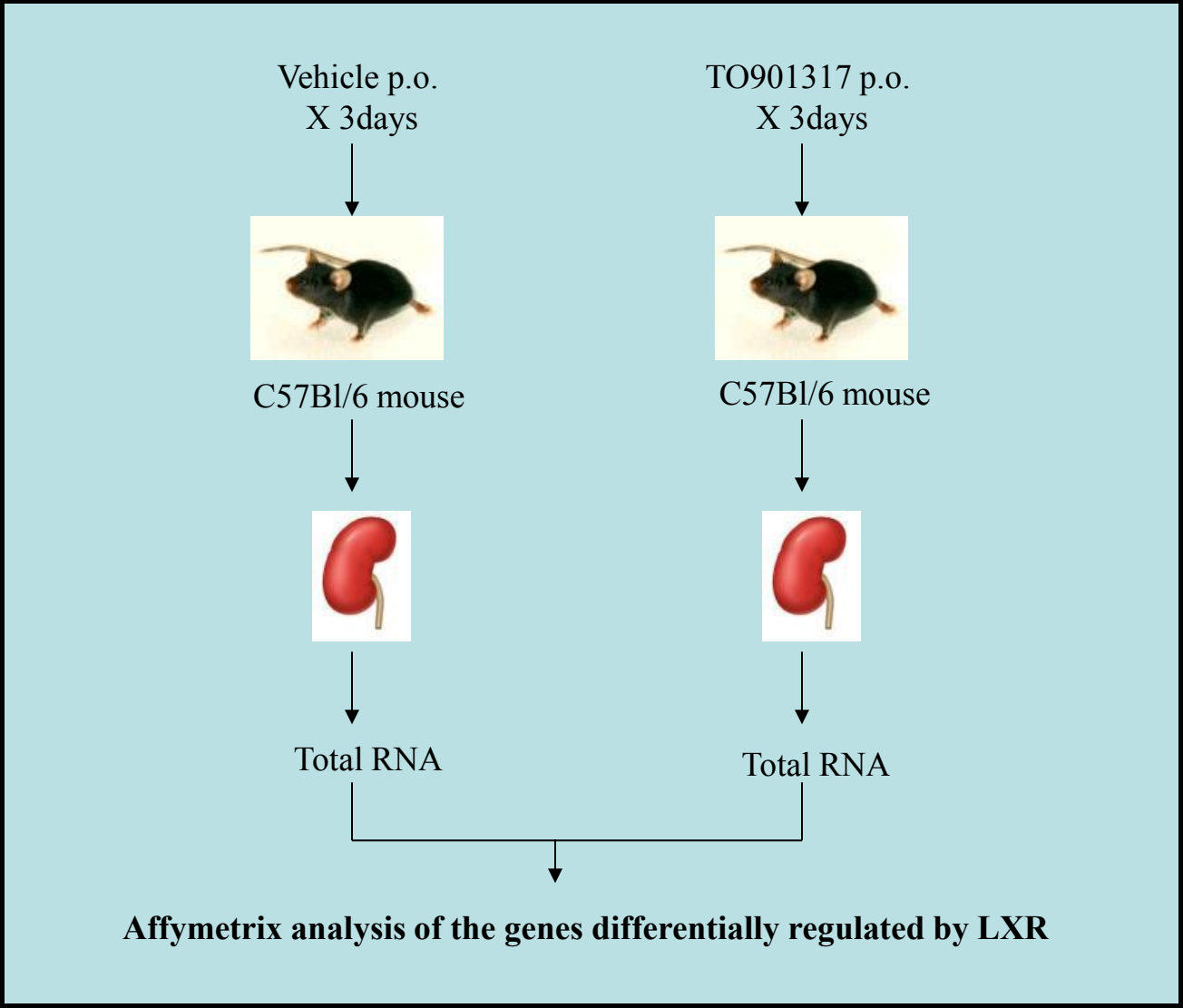
大连医科大学肾脏病中心

大连医科大学心血管病中心

在职博士后计划

guanyf@dmu.edu.cn

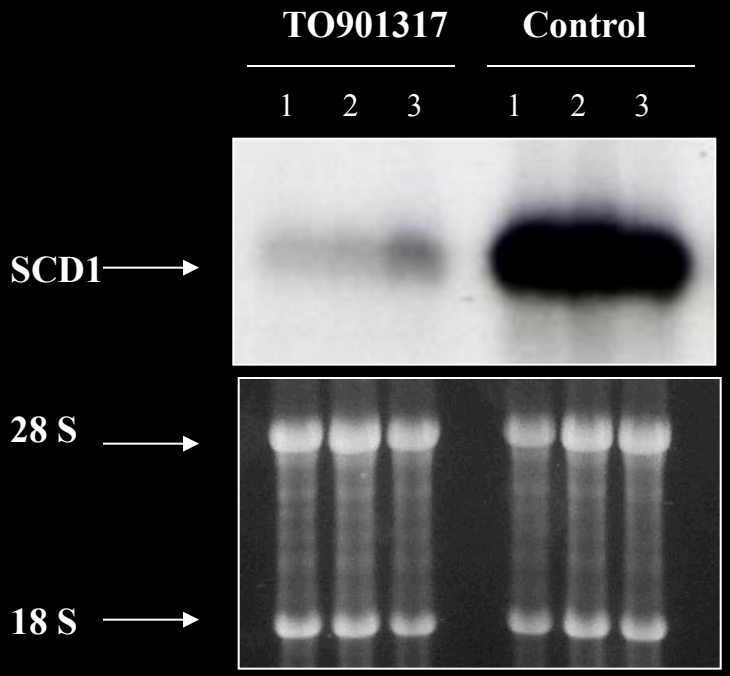
Genomewide Analysis of gene expression profile regulated by LXR in the kidney

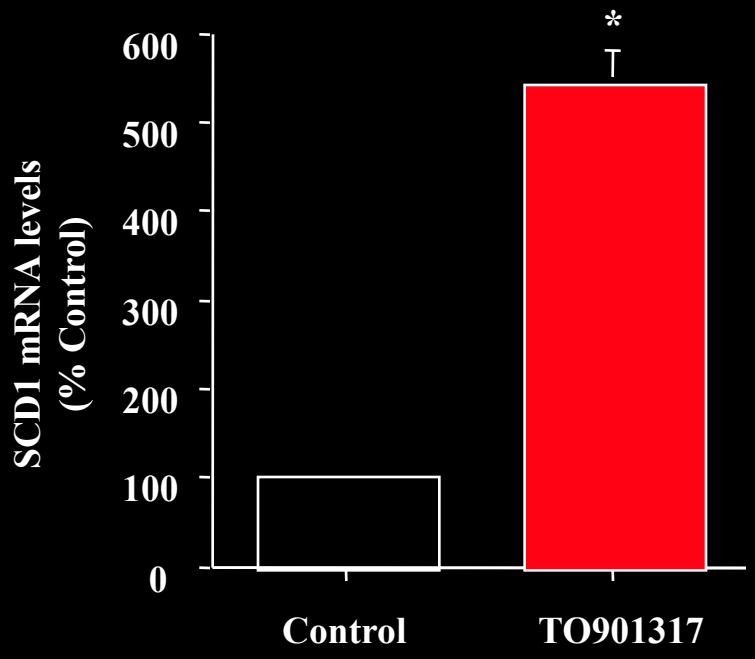


Partial list of genes regulated by TO 901317 in mouse kidney

Name of gene	GenBank accession #	Gene function
Increased genes		
stearoyl CoA desaturase 1 (SCD1)	**M21285**	**fatty acid Δ9-desaturation**
stearoyl CoA desaturase 1 (SCD2)	M26270	fatty acid Δ9-desaturation
PRP39 pre-mRNA processing factor 39 homolog	AV366904	unknown
major urinary protein group 1	M17818	unkown
SREBP-1	AI843895	fatty acid synthase
calpain 5	Y10656	ABCA1 degradation
Decreased genes		
P53 binding protein (P53BP1)	AW048394	cell growth, apoptosis
interleukin-15 (IL-15)	U14332	renal epithelial cells survival
lipocortin I	AV003419	ca++-dependent phospholipid binding protein, apoptosis
Aryl-hydrocarbon receptor (AhR)	M94623	environmental sensor and cell cycle checkpoint
prostaglandin E2 receptor 3 (EP3)	D10204	sodium and water homeostasis
carboxypeptidase	X61232	neuropeptide conversion
cyclin G	L49507	cell cycle
TNFa receptor associated factor (TRAF)	U59864	apoptosis
3-hydroxyisobutyryl CoA hydrolase	AW121399	amino acid catabolism
lipoprotein lipase (LPL)	M63335	triglyceride metabolism
cytochrome p450 7b1	U36993	bile acid synthesis
FBJ osteosarcoma oncogene	V00727	oncogene

Northern blot analysis revealed a marked induction of SCD1 gene expression in the kidneys of mice treated by TO901317





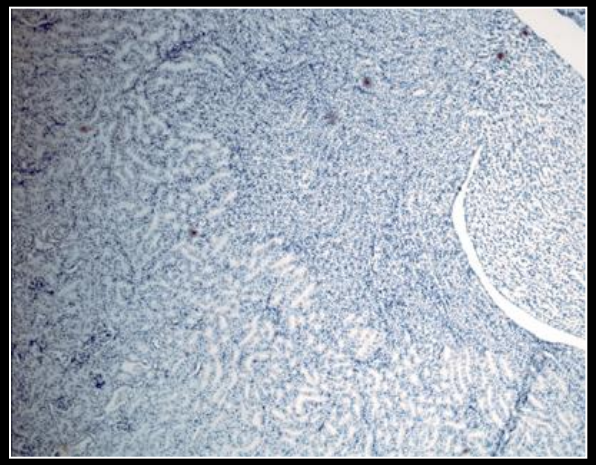
Immunohistochemical studies demonstrating SCD1 protein expression in mouse kidneys

Control (-1° Ab)

vehicle

TO901317

A.



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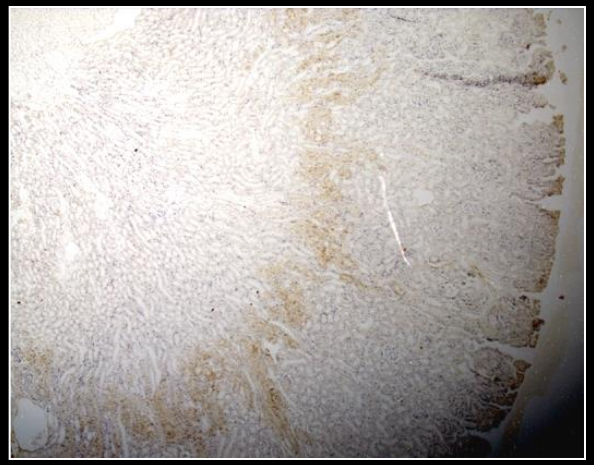
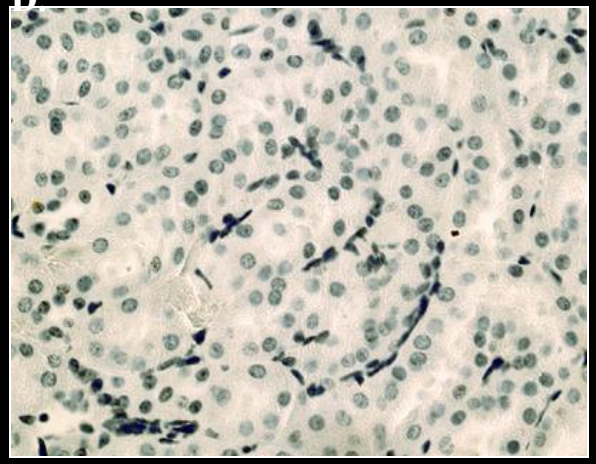


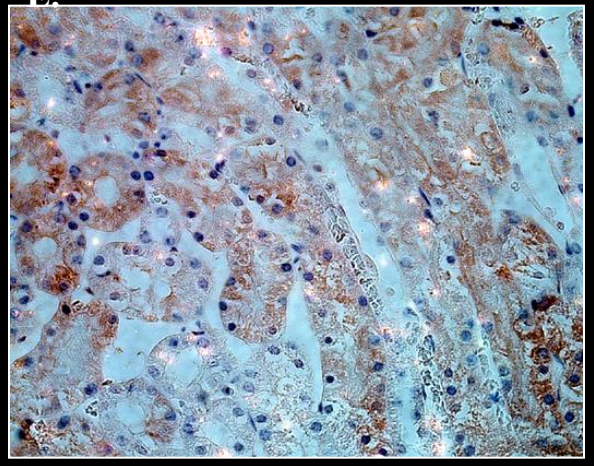
C.

50 X

D.



E.



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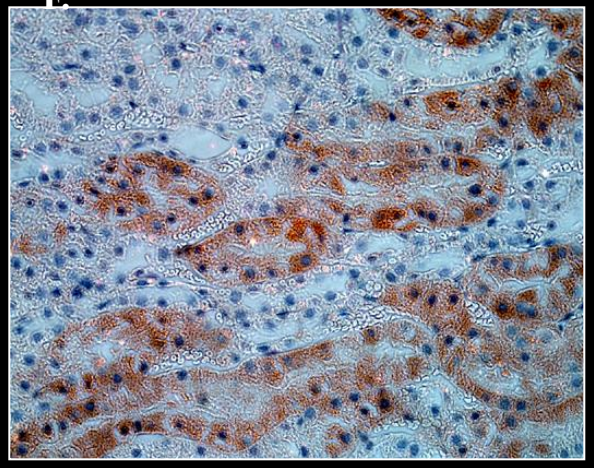
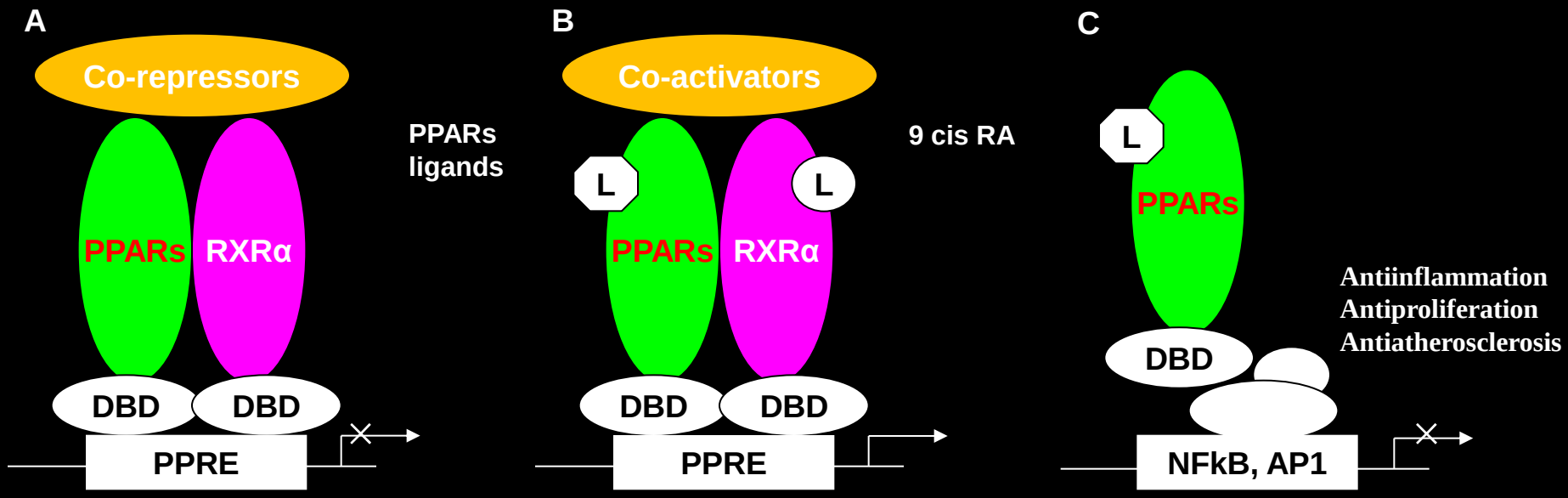


400 X

代谢性核受体PPARs作用模式及功能
Action modes of PPARs



Ligand-independent repression

Ligand-dependent transactivation

Ligand-dependent repression

Ruan X, Zheng F, Guan Y (阮雄中、郑丰、管又飞）. Am J Physiol Renal Physiol 2008