Expanded View Figures

Figure EV1. Characteristics of a mouse model of type 2 diabetic nephropathy.

- А Schema illustrating mouse model of type 2 diabetic nephropathy (DN) using high fat diet (HFD) and a single-dose streptozotocin (50 mg/kg) intraperitoneal injection.
- Increment change of body weight in eNOS^{+/+} ND, eNOS^{+/+} HFD+STZ, eNOS^{-/-} ND and eNOS^{-/-} HFD+STZ. R
- C, D HbA1c% (C) and plasma insulin level (D) change in eNOS^{+/+} ND, eNOS^{+/+} HFD+STZ, eNOS^{-/-} ND and eNOS^{-/-} HFD+STZ after 24 weeks of treatment.
 Periodic acid–Schiff (PAS) staining of sections from eNOS^{+/+} ND, eNOS^{+/+} HFD+STZ, eNOS^{-/-} ND and eNOS^{-/-} HFD+STZ mouse kidneys. Scale bars: 50 μm.
- Urinary albumin/creatinine ratio changes from eNOS^{+/+} ND, eNOS^{+/+} HFD+STZ, eNOS^{-/-} ND and eNOS^{-/-} HFD+STZ mouse. F
- Serum cystatin C changes from eNOS^{+/+} ND, eNOS^{+/+} HFD+STZ, eNOS^{-/-} ND and eNOS^{-/-} HFD+STZ mouse. G

Data information: One-way ANOVA was performed. Data are shown as mean ± SD from groups of eight mice. *P < 0.05, **P < 0.001, ***P < 0.001, ** P > 0.05.







Figure EV1.

Figure EV2. Smad4 LNA administration retards the progression of mouse type 2 diabetic nephropathy.

- A–C Changes in body weight, fasting blood glucose levels and plasma insulin in age-matched, control-LNA (CTL LNA)-treated or Smad4 LNA-treated type 2 diabetic eNOS^{-/-} mice.
- D, E Glucose tolerance test (E) and quantification of glucose tolerance test (D) in age-matched, control-LNA (CTL LNA)-treated or Smad4 LNA-treated type 2 diabetic eNOS^{-/-} mice.

Data information: One-way ANOVA was performed. Data are shown as mean \pm SD from groups of 6 mice.





Figure EV2.



Figure EV3. Smad4 LNA treatment decreases podocyte injury and glomerulosclerosis in type 2 diabetic nephropathy.

A–F Confocal microscopy demonstrated synaptopodin (red, A–C) and collagen IV expression (green, D–F) in age-matched kidney, CTL LNA-treated diabetic nephropathy and Smad4 LNA-treated diabetic nephropathy. Scale bars: 50 µm.



Figure EV4. Smad4 deficiency in podocytes protects mice from type 2 diabetic nephropathy.

A–D Changes in body weight, fasting blood glucose levels, HbA1c and plasma insulin in ND-treated or HFD+STZ-treated eNOS^{-/-} PodCre mice or eNOS^{-/-} PodCre-Smad4^{-/-} mice.

E, F Glucose tolerance test (E) and quantification of glucose tolerance test (F) in ND-treated or HFD+STZ-treated eNOS^{-/-} PodCre mice or eNOS^{-/-} PodCre-Smad4^{-/-} mice.

Data information: One-way ANOVA was performed. Data are shown as mean \pm SD from groups of eight mice. N.S, P > 0.05; ***P < 0.001; ****P < 0.001.

KEGG pathway			
		1.5	Regulated.Type
		1	all
	mmu00010 Glycolysis / Gluconeogenesis		Sample
	mmu00051 Fructose and mannose metabolism	0.5	WT HGvsWT LG
	mmu01200 Carbon metabolism	0	KO_HGvsKO_LG
	mmu01230 Biosynthesis of amino acids	0	KO_HGvsWT_HG
	mmu00230 Purine metabolism	-0.5	KO_LGvsWT_LG
	mmu04922 Glucagon signaling pathway		
	mmu00030 Pentose phosphate pathway	-1	
	mmu04973 Carbohydrate digestion and absorption	-1.5	
	mmu00520 Amino sugar and nucleotide sugar metabolism		
	mmu00500 Starch and sucrose metabolism		
	mmu00970 Aminoacyl-tRNA biosynthesis		
	mmu03010 Ribosome		
	mmu03050 Proteasome		
	mmu04145 Phagosome		
	mmu04974 Protein digestion and absorption		
	mmu04966 Collecting duct acid secretion		
	mmu04512 ECM-receptor interaction		
	mmu00531 Glycosaminoglycan degradation		
	mmu00260 Glycine, serine and threonine metabolism		
	mmu00620 Pyruvate metabolism		
	mmu00190 Oxidative phosphorylation		
	mmu00340 Histidine metabolism		
	mmu00071 Fatty acid degradation		

Figure EV5. Encyclopedia of Genes and Genomes (KEGG) database annotates protein pathways in wild-type or Smad4-deficient podocytes treated with normal glucose (NG) or high glucose (HG).