Expanded View Figures

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

A 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.

B Increment change of body weight in $eNOS^{+/+}$ ND, $eNOS^{+/+}$ HFD+STZ, $eNOS^{-/-}$ ND and $eNOS^{-/-}$ HFD+STZ.

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.

E 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.

F Urinary albumin/creatinine ratio changes from $eNOS^{+/+}$ ND, $eNOS^{+/+}$ HFD+STZ, $eNOS^{-/-}$ ND and $eNOS^{-/-}$ HFD+STZ mouse.

G Serum cystatin C changes from $eNOS^{+/+}$ ND, $eNOS^{+/+}$ HFD+STZ, $eNOS^{-/-}$ ND and $eNOS^{-/-}$ HFD+STZ mouse.

Data information: One-way ANOVA was performed. Data are shown as mean ± SD from groups of eight mice. *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$, ****$P < 0.0001$, N.S, $P > 0.05$.

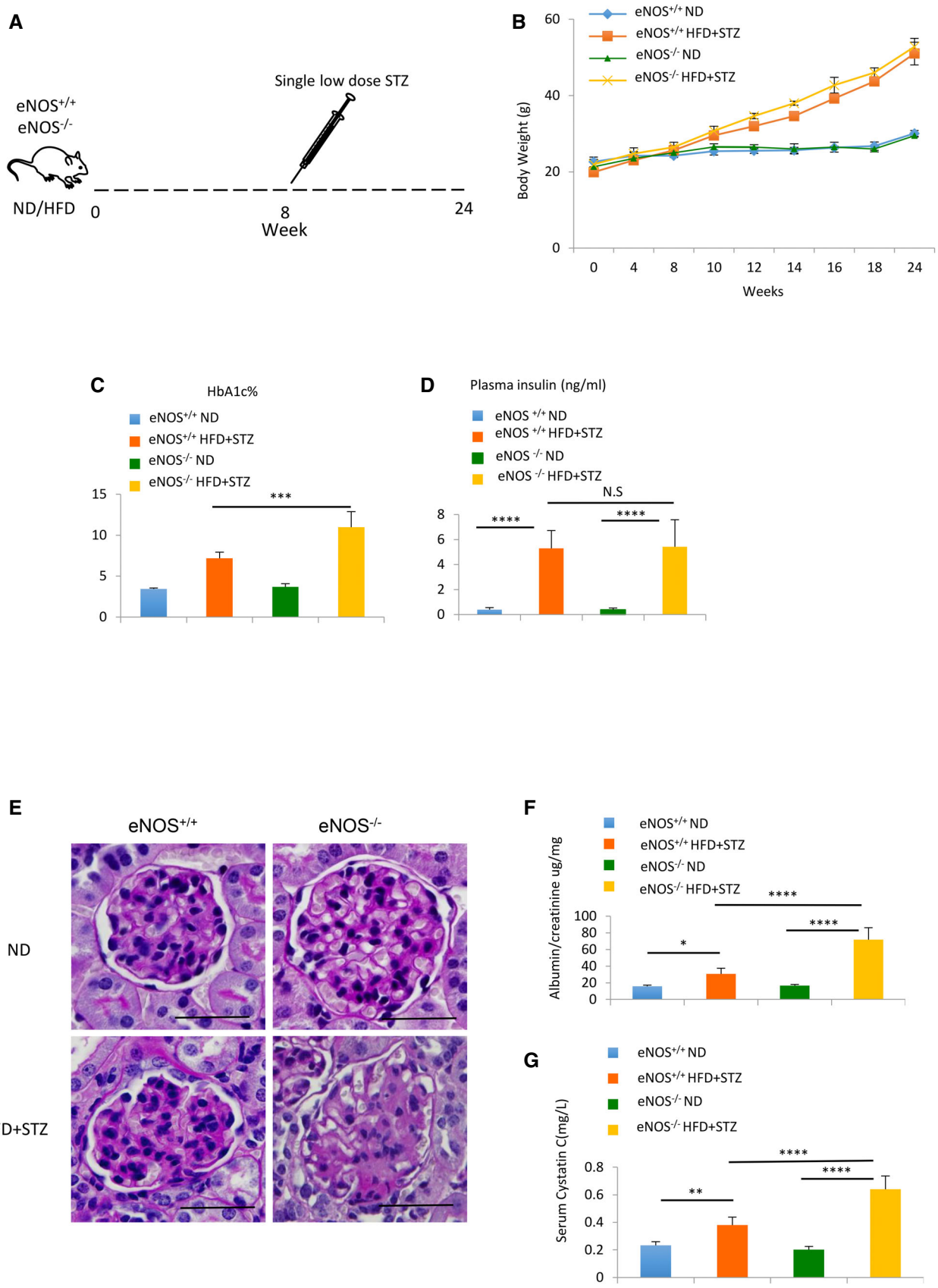

Figure EV1.

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 ± SD from groups of 6 mice.

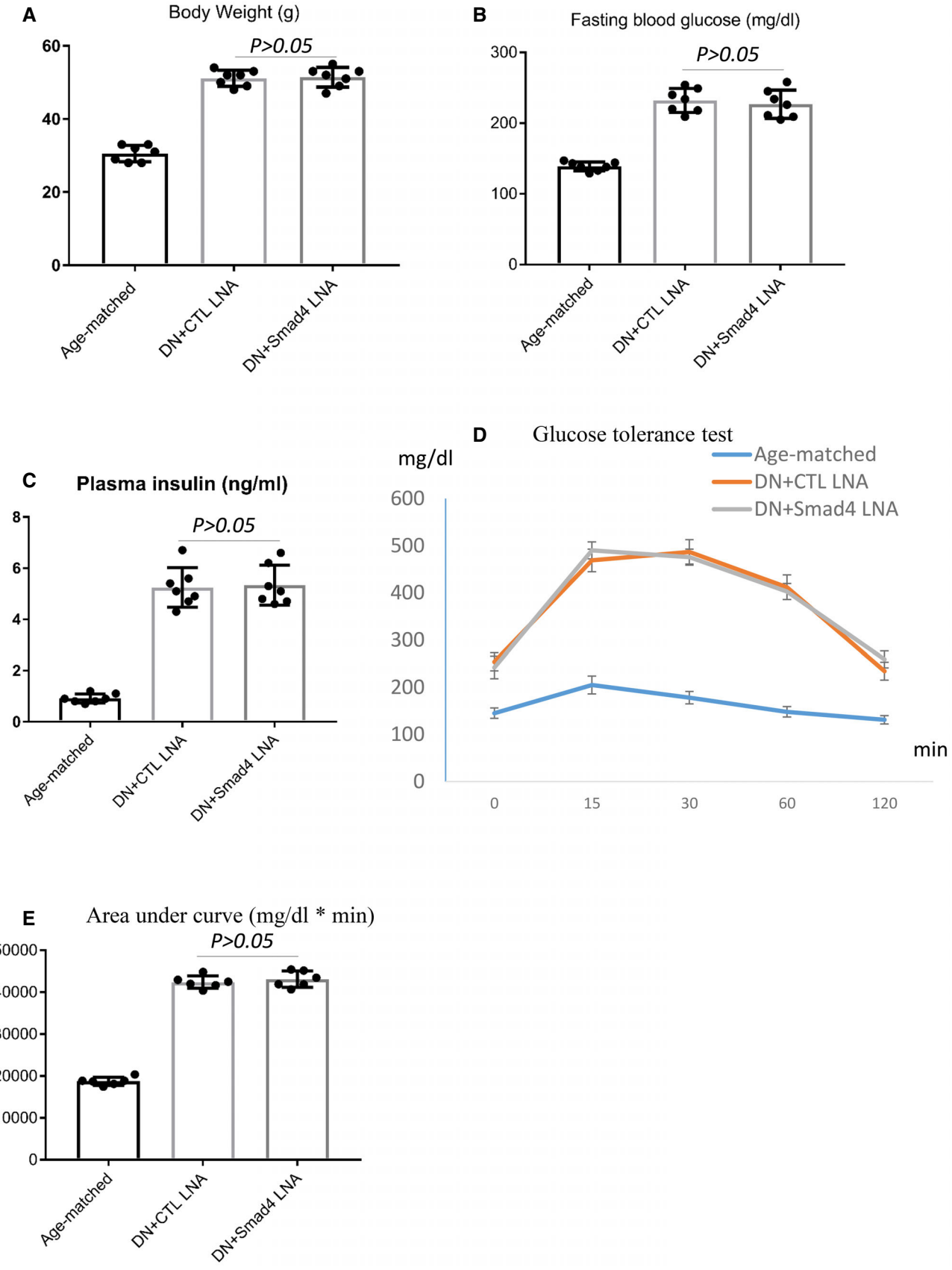

Figure EV2.

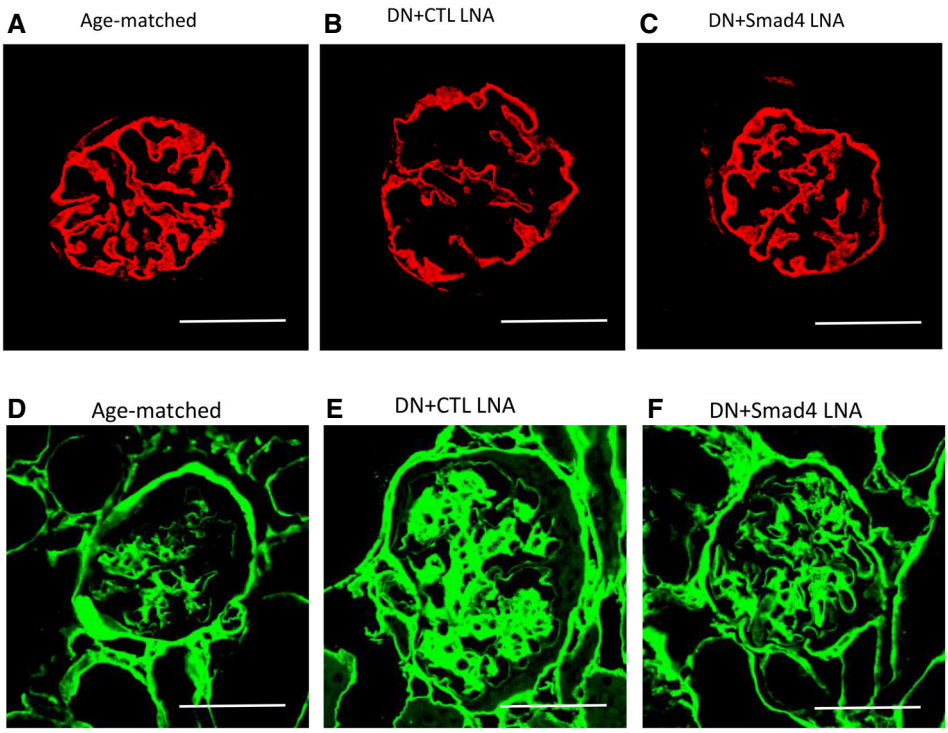

Figure EV3. Smad4 LNA treatment decreases podocyte injury and glomerulosclerosis in type 2 diabetic nephropathy.

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.

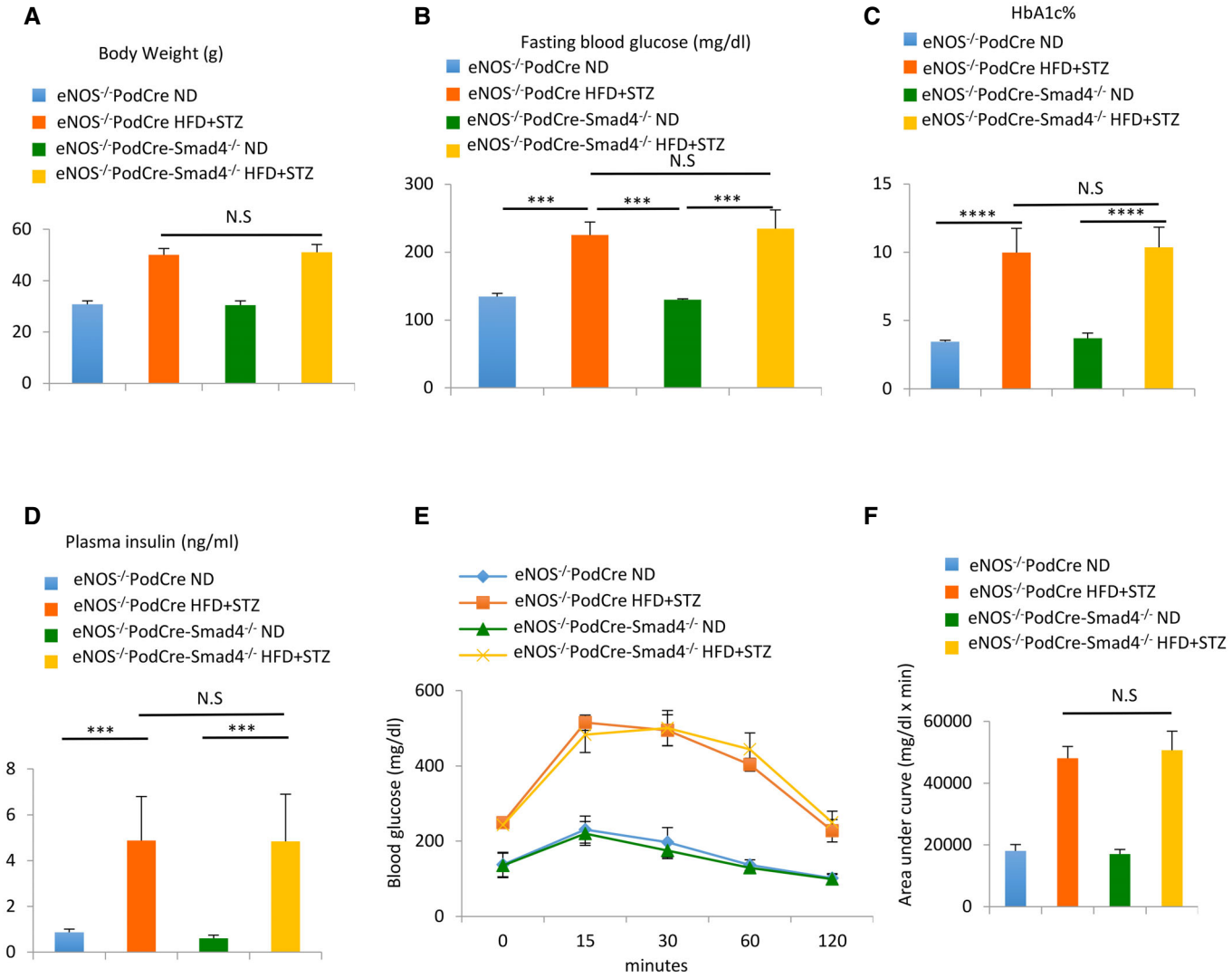

Figure EV4. Smad4 deficiency in podocytes protects mice from type 2 diabetic nephropathy.

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 ± SD from groups of eight mice. N.S, $P > 0.05$; ***$P < 0.001$; ****$P < 0.0001$.

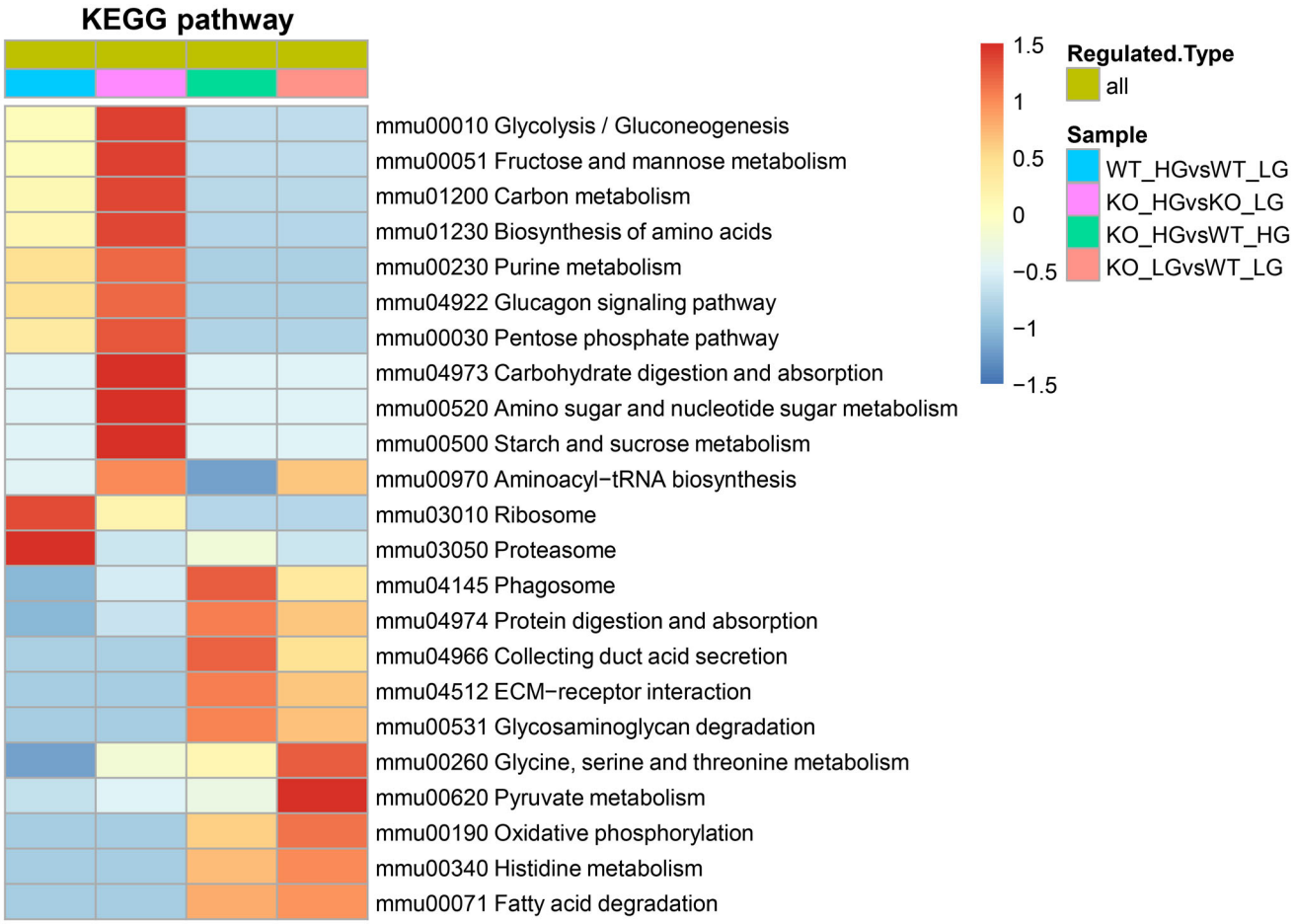

Figure EV5. Encyclopedia of Genes and Genomes (KEGG) database annotates protein pathways in wild-type or Smad4-deficient podocytes treated with normal glucose (NG) or high glucose (HG).