Supplementary Figure S1. Images of representative glomeruli of A) healthy controls, B) T2D without SGLT2i treatment [T2Di(-)], and C) T2D with SGLT2i treatment [T2Di(+)] from PAS-stained 2-3 micrometer thick formalin-fixed, paraffin-embedded sections. Scale bars are 50 micrometers.



Supplementary Figure S2: Quality control for single-cell RNA sequencing

A) Cell specific markers used to define cell clusters. B) HC, T2Di(-) and T2Di(+) contributed to each cell cluster. Abbreviations: PT - proximal tubule, DTL - descending thin limb, ATL - ascending thin limb, TAL- thick ascending limb, DCT - distal convoluted tubule, CNT - connecting tubule, IC - intercalated cells, PC - principal cells, tPC-IC transitioning intercalated/principal cells, EC - endothelial cells, vSMC/MC/Fib vascular smooth muscle cells/mesangial cells/fibroblasts, PEC - parietal epithelial cells, POD - podocytes, MAC - macrophages, MON - monocytes, B - B cells, NKT/NKCT - Natural Killer T Cells/Natural Killer Cells with T cells





Β.

Supplemental Figure S3. Anatomic and cell state annotations for proximal tubule sub-clusters

A-C) Transcriptional profiles from cells from HC, T2Di(-), or T2Di(+) were analyzed for proximal tubule (PT) biomarkers for compartments S1, S2, or S3, from the KPMP Consortium*. Compartment-specific transcripts were more abundant in clusters PT-1 through PT-3 (A) than PT-4 (B) or PT-5 (C). D) Adaptive/maladaptive state biomarkers defined by KPMP for PT-1 through PT-5. E) Cell cycling state biomarkers defined by KPMP for clusters PT-1 to PT-5. F) Degenerative state biomarkers from the KPMP for clusters PT-1 through PT-5.



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Supplementary Figure S4. A)Bioinformatic pipeline describing the analysis of scRNAseq data from the three groups, HC, T2Di(-) and T2Di(+). **B)** Disease associated transcriptional differences when comparing T2Di(-) and HC.



B. Altered expression in type 2 diabetes (T2Di(-) vs HC)



Supplementary Figure S5: Protein-protein interaction networks of transcriptional alterations in PT with SGLT2 inhibition. Protein-protein interaction networks in all PT clusters comparing A)T2Di(-) to HC, B)T2Di(+) to T2Di(-) and C) T2Di(+) to HC. Each dot represents an individual gene and is color coded for any gene with a significant logFC (red: 0 to 0.1 and blue: -0.1 to 0 logFC). Comparison between T2Di(+) to HC (panel C) shows that SGLT2 inhibition retains some differences from HC.

A. T2Di(-) to HC



Supplementary Figure S6: Differential effects with SGLT2i on PT cells, with and without SLC5A2

expression. A) Enriched pathways from transcripts suppressed with SGLT2i in PT cells expressing SLC5A2 expression (PT+). B) Enriched pathways from transcripts suppressed with SGLT2i in PT cells with no detectable SLC5A2 expression (PT-). C) Enriched pathways from transcripts enhanced with SGLT2i in PT- cells. There were too few enhanced transcripts with SGLT2i in PT+ cells for an enrichment analysis.



A. Enriched pathways in SGLT2 inhibitor suppressed transcripts in PT+ cells (N=605)

B. Enriched pathways in SGLT2 inhibitor suppressed transcripts in PT- cells (N=482)



C. Enriched pathways in SGLT2 inhibitor enhanced transcripts in PT- cells (N=265)



Supplementary Figure S7: Reactome enrichment analysis for: A) enhanced transcripts in DTL; B) suppressed transcripts in DTL; C) enhanced transcripts in PC; D) suppressed transcripts in PC; E) enhanced transcripts in IC; and F) suppressed transcripts in IC

A. Enriched pathways in SGLT2i suppressed transcripts in DTL (N=4586)



C. Enriched pathways in SGLT2i suppressed transcripts in PC (N=1335)



Collagen formation Homo sapiens R-HSA-14 Extracellular matrix organization Homo se Non-integrin membrane-ECM interactions H: Intra-Golgi and retrograde Golgi-to-ER t Syndecan interactions Homo sapiens R-HSA: Nuclear Receptor transcription pathway H Bile acid and bile salt metabolism Homo RA biosynthesis pathway Homo sapiens R-H. Assembly of collagen fibrils and other ma Transport of glucose and other sugars, b. Interferon Signaling Homo sapiens R-HSA-Hemostasis Homo sapiens R-HSA-10958 Membrane Trafficking Homo sapiens R-HSA-Transport of organic anions Homo saniens SMAD2/3 Phosphorylation Motif Mutants in Choline catabolism Homo sapiens R-HSA-67.

E. Enriched pathways in SGLT2i suppressed transcripts in IC (N=4477)



B. Enriched pathways in SGLT2i enhanced transcripts in DTL (N=325)





D. Enriched pathways in SGLT2i enhanced transcripts in PC (N=829)





F. Enriched pathways in SGLT2i enhanced transcripts in IC (N=102)

nse to metal ions Homo sapiens R-HS. Metallothioneins bind metals Homo sapien. Constitutive Signaling by Aberrant PI3K NCAM signaling for neurite out-grow PI5P, PP2A and IER3 Regulate PI3K/AKT Si. Gastrin-CREB signalling pathway via PKC PI3K/AKT Signaling in Cancer Homo sapien. Negative regulation of the PI3K/AKT netw. naling by PDGF Homo sapiens R-HSA-186. IRS-mediated signalling Homo sapiens R-H. Insulin receptor signalling cascade Homo. IGF1R signaling cascade Homo sapiens R-H. Signaling by Type 1 Insulin-like Growth IRS-related events triggered by IGF1R Ho. FCERI mediated MAPK activation Homo sapi Signaling by Insulin receptor Homo sapie. GRB2 events in EGFR signaling Homo sapie SHC1 events in EGFR signaling Homo sapie SOS-mediated signalling Homo sapiens R-H. SHC1 events in ERBB4 signaling Homo sapi



5.0 Gene count

Supplementary Figure S8: Transcriptional alterations in human PT cells and mouse kidney cortex, with SGLT2 inhibitors. Significantly perturbed transcripts in central metabolism pathways were similar in human PT cells and mouse kidney cortex with SGLT2i treatment. In mice, db/m=non-hypertensive, non-diabetic control mice; db/db= diabetic mice; SGLT2i=SGLT2i treated diabetic mice.



Supplementary Table S1. Exclusion criteria for percutaneous kidney biopsy

Additional exclusion criteria for those undergoing kidney bi	iops
Evidence of bleeding disorder or complications from bleeding	
Use of aspirin, NSAIDS or other blood thinner that cannot be safely stopped for a sufficient time period before and after the biopsy so as add no additional risk of bleeding	s to
Blood urea nitrogen (BUN) > 80 gm/dL	
INR > 1.4	
PTT > 35 seconds	
Hemoglobin (Hb) < 10 mg/dL	
Platelet count < 100,000 / µL	
Uncontrolled or difficult to control hypertension (> 150/90 mmHg at day of biopsy)	the
eGFR < 40 mL/min/1.73m ²	
Single kidney (either by history, documented by prior imaging or ultrasound performed prior to the biopsy)	
> 2 cm discrepancy between left and right kidney sizes based on larg longitudinal diameter determined by US performed prior to the biop	est sy.
Kidney size: One or both kidneys < 9 cm	
Hydronephrosis or other important renal ultrasound findings such as significant stone disease	\$
Any evidence of a current urinary tract infection as indicated on day biopsy	of
Clinical evidence of non-diabetic renal disease	
Positive urine pregnancy test or pregnancy	

Supplementary Table S6: List of MTORC1 pathway List of MTORC1 pathway transcripts, based on Reactome database (R-HSA-165159), used in determining pathway score.

mIOR signalling Homo sapiens
STRADA
STRADB
RPS6
TSC2
TSC1
PRKAB1
PRKAB2
MTOR
PPM1A
RRAGB
RRAGA
RRAGD
RHEB
RPS6KB1
RRAGC
AKT1S1
EIF4G1
LAMTOR1
LAMTOR3
LAMTOR2
EIF4EBP1
PRKAG2
PRKAG3
PRKAG1
PRKAA1
STK11
RPTOR
EEF2K
MLST8
AKT1
AKT2
EIF4E