SUPPLEMENTARY DATA FILE

Supplementary Tables

- **Supplementary Table 1: Primer sequences for genotyping**
- **Supplementary Table 2: Primer sequences for qPCR**

Supplementary Figure Legends

Supplementary File 1

Supplementary Table 1. Primer sequences for genotyping

Gene	Forward primer	Reverse primer
db/db	CATTCAAACCATATTTAGGTTTGTGT	AGAACGGACACTCTTTGAAGTCTC
Sco2	TTGCCACCTTTGTTCTTTTCCAGG	TTCCGCACCACCTGCACTAGCTTTTCAAGC

Supplementary Table 2. Primer sequences for qPCR

Gene	Forward primer	Reverse primer
Sco2	AGCTCTCTCAGTTCAAACCCC	GCAGTCTAGTTCTTAGCCCAGG
Klf2	CATGTGCCGTTTCATGTGC	CAAGACCTACACCAAGAGTTCG
Icam1	GTGATGCTCAGGTATCCATCCA	CACAGTTCTCAAAGCACAGCG
Vcam1	TGGTCGCGGTCTTGGGAGCCT	CCGGCTTCCCAACCTCCAGGGG
Vegfr2	TTGAAATCGACCCTCGGCAG	TACAAGTGCTCGTACCGGG
Cd31	AAGCCAACAGCCATTACGGTTA	TAAGGGAGCCTTCCGTTCTCTT
Ehd3	CAAGAGCAGGGTTAGGCACT	CTAATGAACGGGAGGCTGAG
Wt1	GAGAGCCAGCCTACCATCC	GGGTCCTCGTGTTTGAAGGAA
Podocin	CTTGGCACATCGATCCCTCA	CGCACTTTGGCCTGTCTTTG

Supplementary Figure Legends

Supplementary Figure 1. Baseline data in wildtype, *Sco2*$^{KO/KI}$*, and Sco2*$^{KI/KI}$ mice. (*A*) *Sco2* mRNA expression relative to the wildtype mice. (n=5, *P<0.05, **P<0.01, Mann-Whitney *t*-test). (*B*) Quantification of COX activity (10 HPF/sample, n=3 per group, Kruskal-Wallis test with Dunn posttest; *P<0.05). (*C*) Blue Native-Page to determine the amount of native complex IV with representative image of three independent experiments with identification of all 5 complexes shown. (*D*) Urinary albumin to creatine ratio (uACR) (n=5, Kruskal-Wallis test with Dunn posttest). *E*: Representative images of paraffin-embedded sections of kidney stained with Periodic acid-Schiff, and heart and liver stained with Hematoxylin & Eosin (20X) (Scale bar = 50 μm).

Supplementary Figure 2. Quantification of ultrastructural glomerular changes in diabetic *Sco2* hypomorphs (*Sco2*$^{KO/KI}$;*db/db*, *Sco2*$^{KI/KI}$;*db/db*) mice and *db/db* mice. Quantification of (*A*) GBM thickness and (*B*) foot process width between slit diaphragm is shown between all groups (50 measurements per mouse, n=3 per group; **P<0.01, ****P<0.0001; Kruskal-Wallis test with Dunn posttest).

Supplementary Figure 3. snRNA-seq QC parameters and UMAP plot by unsupervised clustering. (*A-B*) The number of genes (nFeatures), UMIs (nCount), and percentage of mitochondrial transcripts (percent.mt) are shown as a violin and feature plots. *(C)* Uniform Manifold Approximation and Projection (UMAP) plot illustrates all clusters identified by unsupervised clustering.

Supplementary Figure 4. Subclustering of the endothelial cluster is reflective of glomerular endothelial cells (GEnCs). *(A)* Dot plot of key GEnC marker genes in the endothelial subclusters. Violin plot of *(B)* upregulated and *(C)* downregulated genes in the endothelial subclusters. *Kdr*: *Kinase insert domain receptor*, *Ehd3*: *EH Domain Containing 3, Gpx3*: *Glutathione peroxidase 3*, *Zbtb16*: *Zinc finger and BTB domain containing 16*, *Hspg2*: *Heparan sulfate proteoglycan 2*, *Plvap*: *Plasmalemma vesicle associated protein*, *Igfbp5*: *Insulin like growth factor binding protein 5, Malat1*: *Metastasis associate lung adenocarcinoma transcript 1*, *Mecom*: *MDS1 and EVI1 complex locus*, *Eln*: *Elastin*, *Thsd4*: *Thrombospondin type 1 domain containing 4*, *St3gal4*: *Sialyltransferase 4C (beta-galactoside alpha-2,3-sialyltransferase 4)*, *Ptprj*: *Protein tyrosine phosphatase receptor type J*.

Supplementary Figure 5. Reactome, Wikipathway, and KEGG enrichment analysis of upregulated genes in the *Sco2*$^{KO/KI}$*;db/db* mice as compared to *db/db* mice in cell clusters with a minimum of 40 differentially expressed upregulated genes. *(A)* PT-S1-S2-1, *(B)* PT-S1-S2-2, *(C)* PT-S3, *(D)* PT-S3/LH(DL), *(E)* LH(AL), *(F)* IC-B, *(G)* CNT, *(H)* DCT, *(I)* Mes. PT: proximal tubule, LH(AL): Loop of Henle (Ascending loop), LH(DL): Loop of Henle (Descending loop), IC: intercalated cell, CNT: connecting tubule, DCT: distal convoluted tubule, Mes: mesangial. Reactome: dark gray bars, Wikipathway: grey bars, KEGG: black bars

Supplementary Figure 6. Reactome, WikiPathway, and KEGG enrichment analysis of downregulated genes in the *Sco2*$^{KO/KI}$*;db/db* mice as compared to *db/db* mice in cell clusters with a minimum of 40 differentially expressed downregulated genes. *(A)* PT-S1-S2-1, *(B)* PT-S1-S2-2, *(C)* PT-S3, *(D)* LH(AL), *(E)* CNT. PT: proximal tubule, LH(AL): Loop of Henle (Ascending loop), CNT: connecting tubule. Reactome: dark gray bars, Wikipathway: grey bars, KEGG: black bars

Supplementary Figure 7. SnRNA-seq with enrichment analysis demonstrates a decrease in cell-matrix adhesion and complement activation genes in *Sco2*$^{KO/KI}$*;db/db* as compared to *db/db* mice*. (A)* Violin plot of key downregulated genes in the endothelial cluster between *Sco2*$^{KO/KI}$*;db/db* and *db/db* mice. *(B)* WikiPathway, Reactome, and KEGG enrichment analysis in downregulated genes in the *Sco2*$^{KO/KI}$*;db/db* mice as compared to *db/db* mice in the endothelial cluster. *Malat1*: *Metastasis associate lung adenocarcinoma transcript 1*, *Mecom*: *MDS1 and EVI1 complex locus*, *Eln*: *Elastin*, *Thsd4*: *Thrombospondin type 1 domain containing 4*, *St3gal4*: *Sialyltransferase 4C (beta-galactoside alpha-2,3-sialyltransferase 4), Ptprj: Protein tyrosine phosphatase receptor type J.*

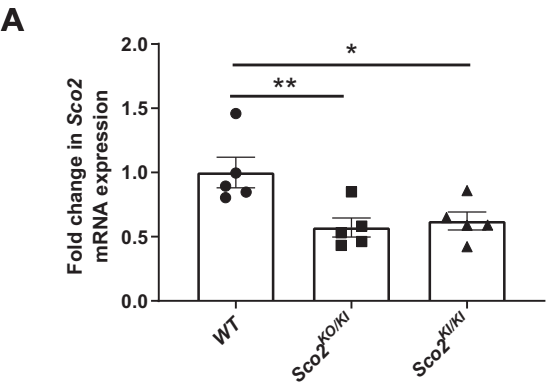
Supplementary Figure 8. Knockdown of *Sco2* in glomerular endothelial cells (GeNCs). *(A)* The relative mRNA expression to β-actin of GeNC markers (*Cd31* and *Ehd3*) and podocyte markers (*Wt1* and *Pod*) in GEnCs. *(B)* Fold change in *Sco2* mRNA expression in *Sco2*-shRNA and *EV*-shRNA GeNCs (n=4, *p<0.05, Mann-Whitney *t*-test). *(C)* Fold change in *Vegfr2*, *Klf2*, *Icam1*, and *Vcam1* mRNA expression in *Sco2*-shRNA and *EV*-shRNA GeNCs (n=4; *P<0.05, **P<0.01; Mann-Whitney *t*-test, ND: Not detected). *Cd31*: *Cluster of differentiation 31*, *Ehd3*: *Eps15 homology domain-containing 3*, *Wt1*: *Wilms' tumor 1*, and *Pod*: *Podocin*.

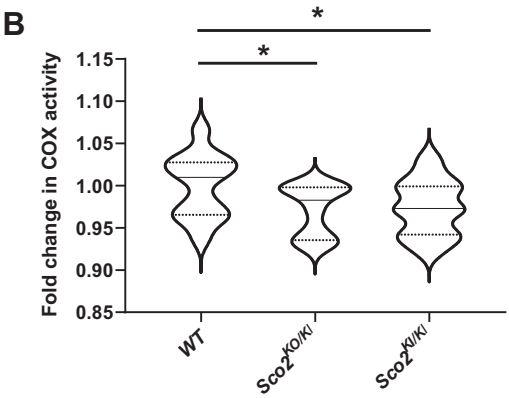
Supplementary Figure 9. *(A)* Representative images of immunofluorescence staining for SCO2. Dashed white line shows the glomerular region. Scale bar = 25 μm. *(B)* Representative images of immunohistochemistry for COX activity. Dashed black line shows the glomerular region. Scale bars = 20 μm. *(C)* Representative images of immunofluorescence staining for DAPI and 8-oxoG. Dashed white line shows the glomerular region. Scale bar = 25 μm.

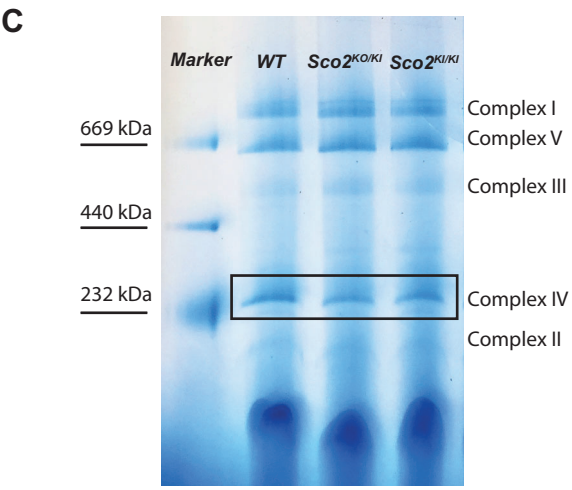
Supplementary Figure 10. *(A)* Representative images of immunostaining for TOMM20, Isolectin, DAPI (arrow indicates the co-expression of TOMM20 and Isolectin) and *(B)* mt-CO2, Isolectin, DAPI (arrow indicates the co-expression mt-CO2 and Isolectin; arrowhead indicate the non-specific mt-CO2 staining). Scale bar = 25 μm.

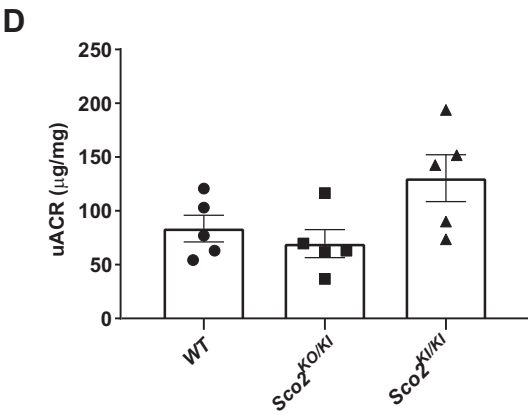
Supplementary Figure 11. *(A)* Quantification of non-glomerular COX activity (n=3 per group). *(B)* Quantification of non-glomerular 8-oxoG staining (n=3 per group, Kruskal-Wallis test with Dunn posttest; ***P<0.001, ****P<0.0001).

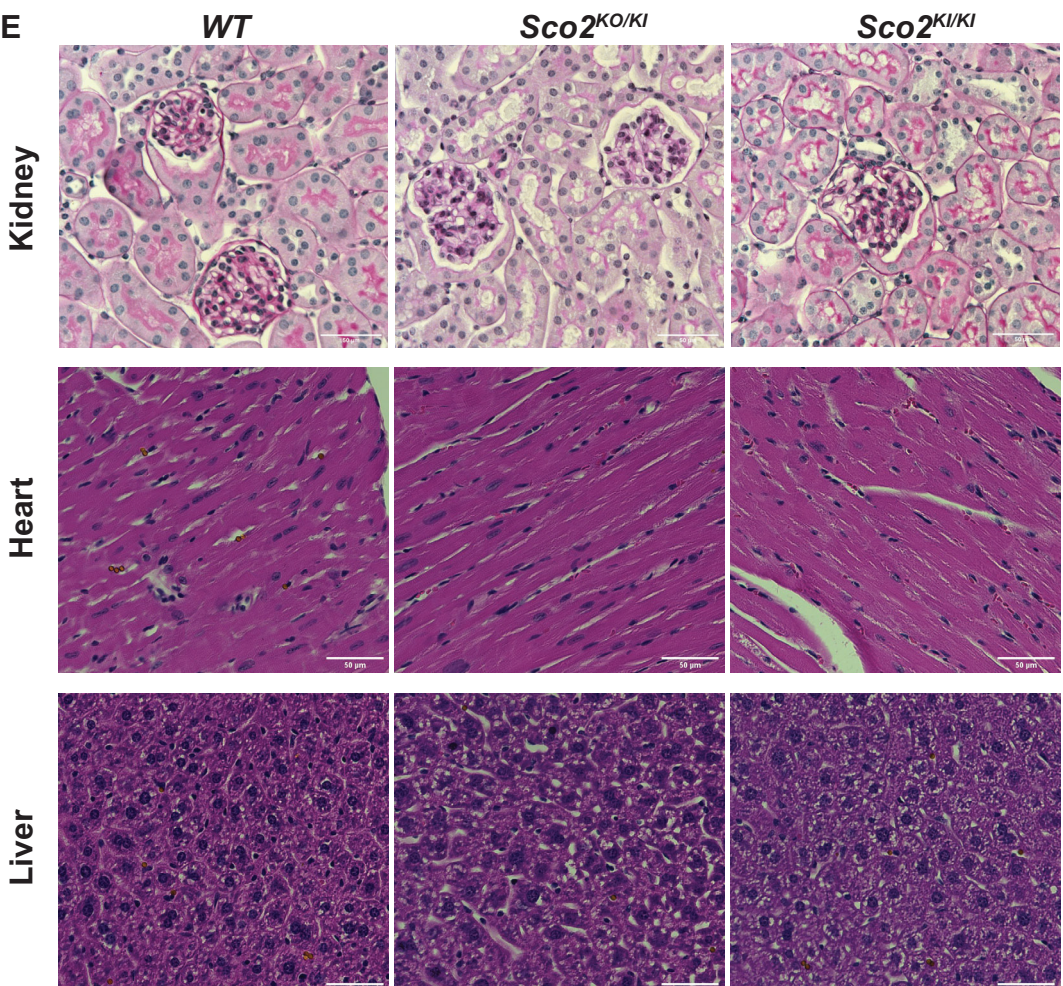
Supplementary Figure 1











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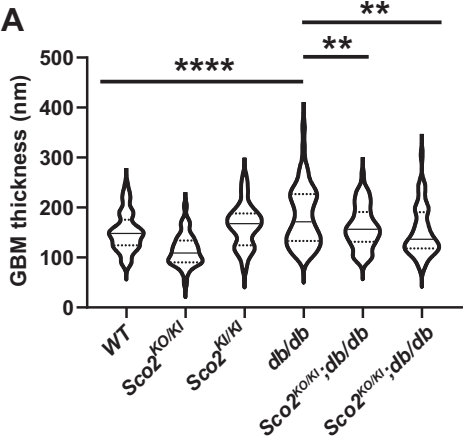

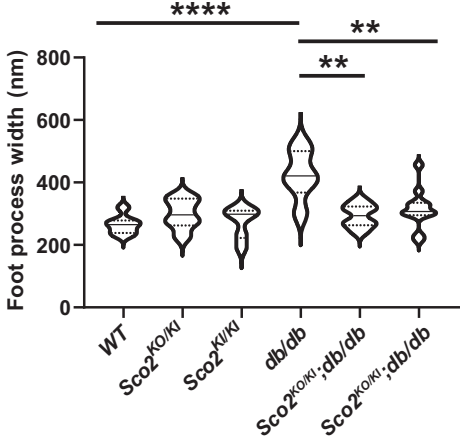

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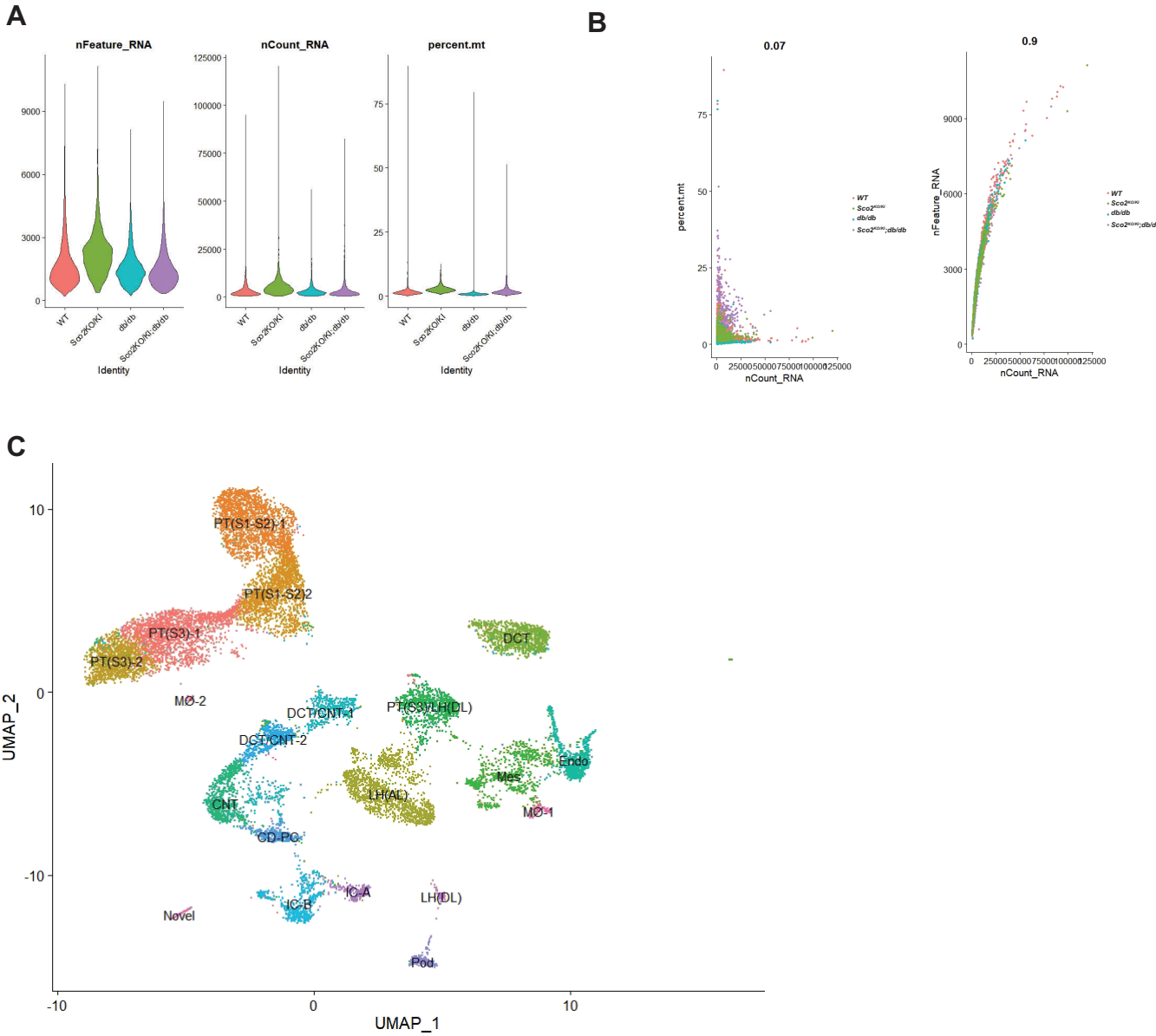

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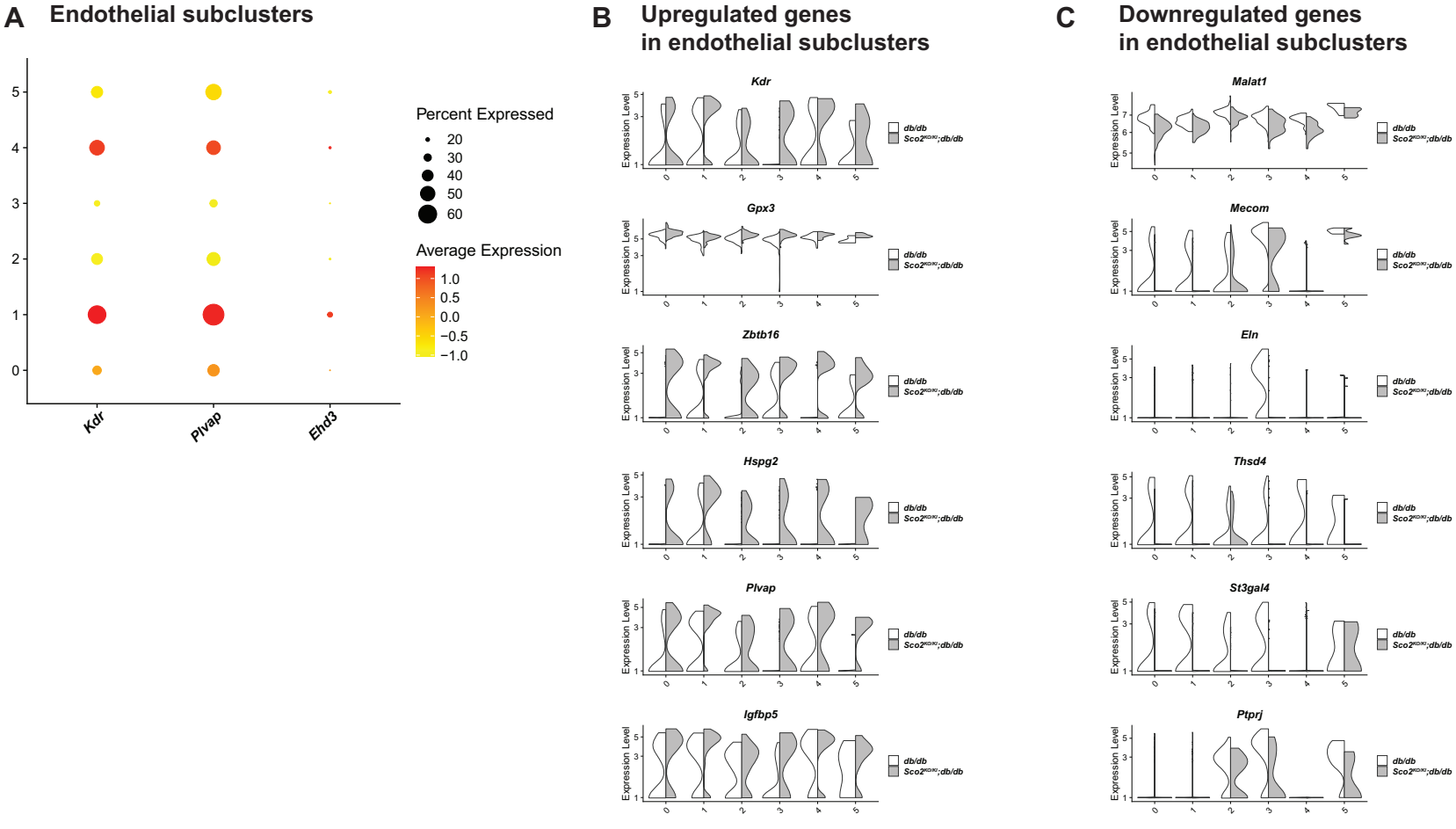

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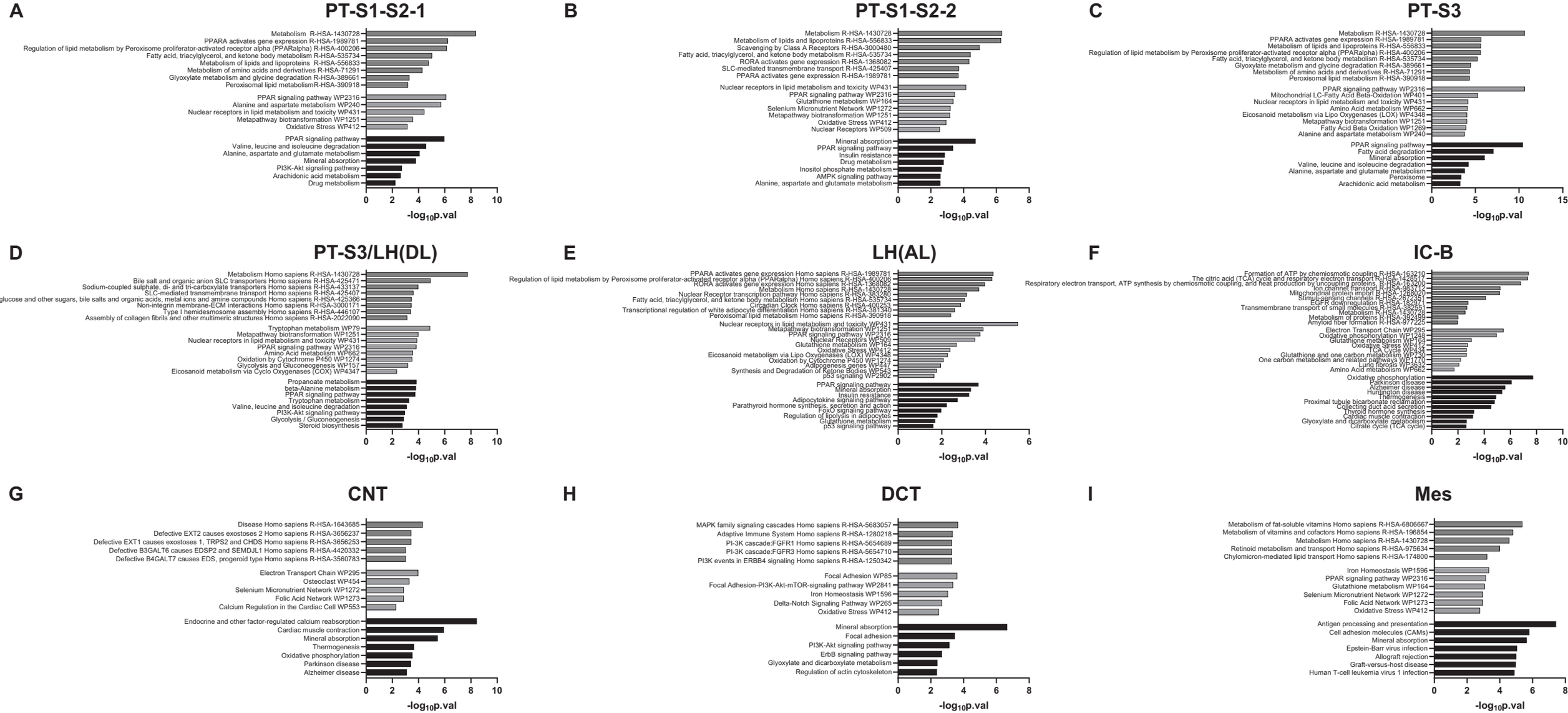

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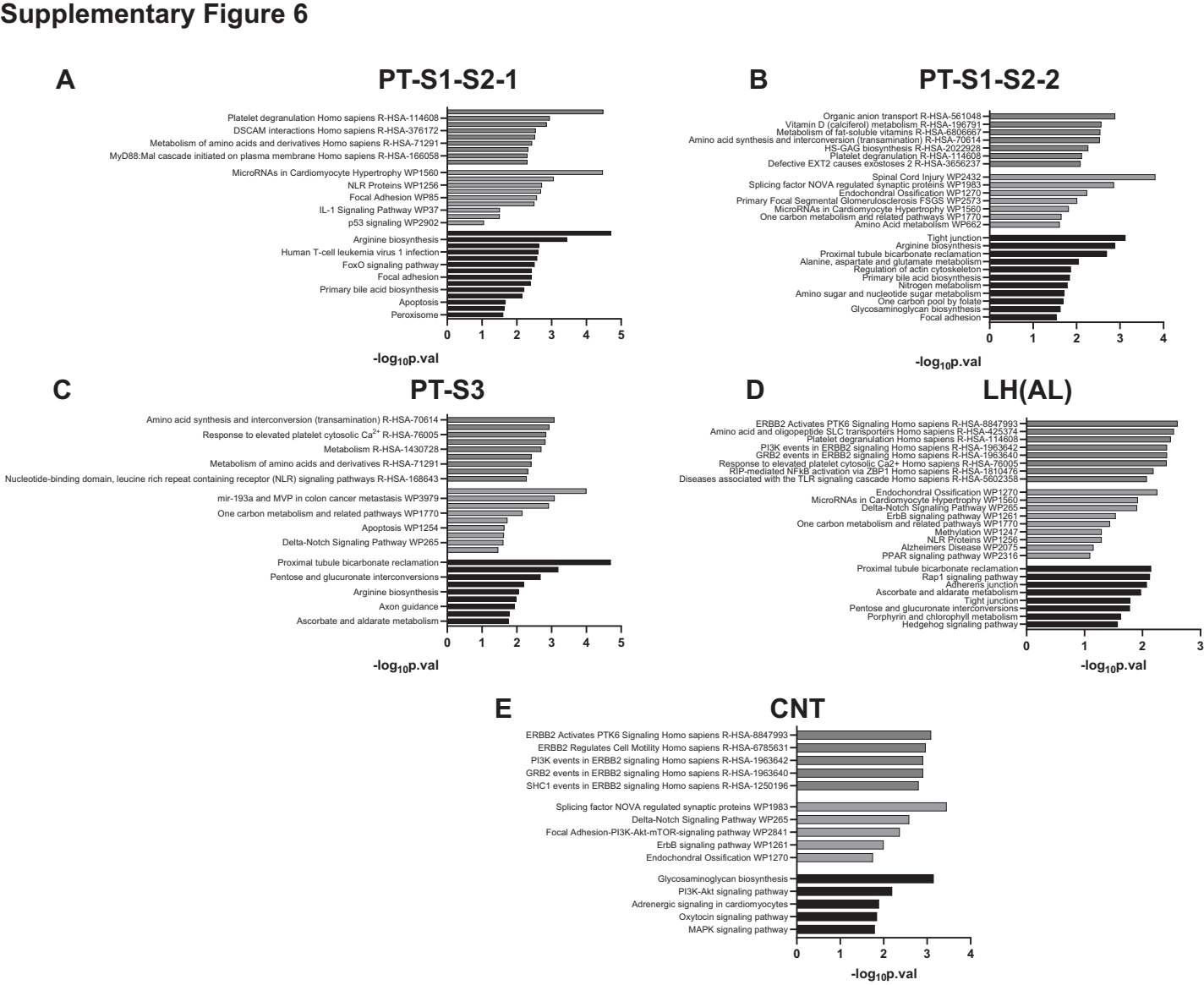

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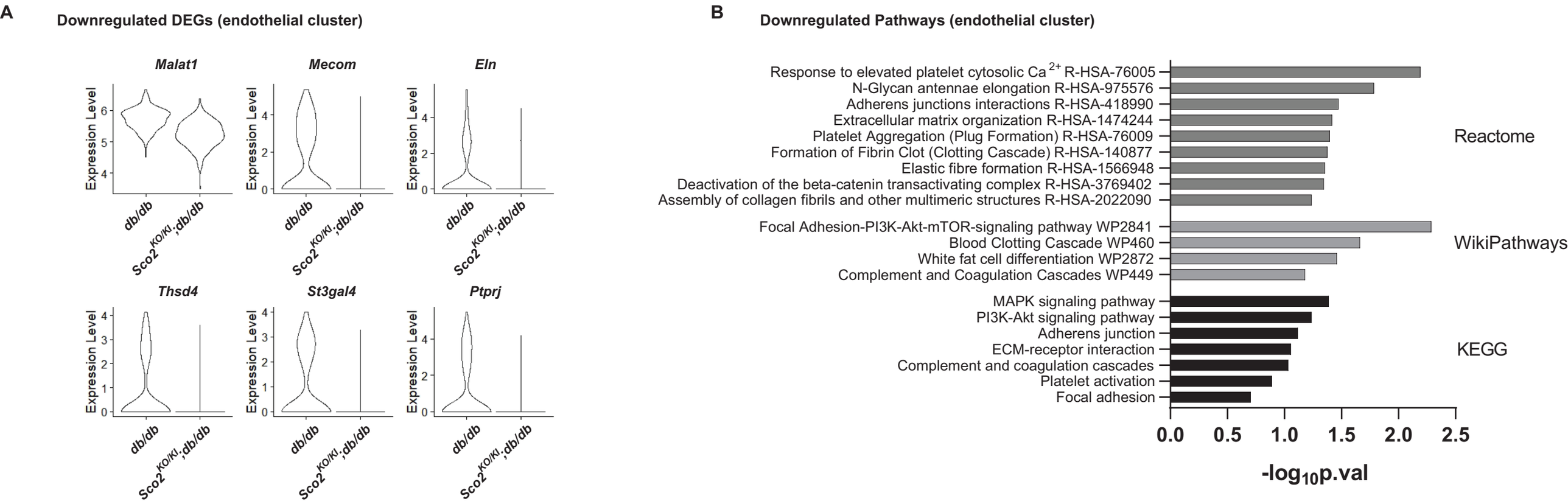

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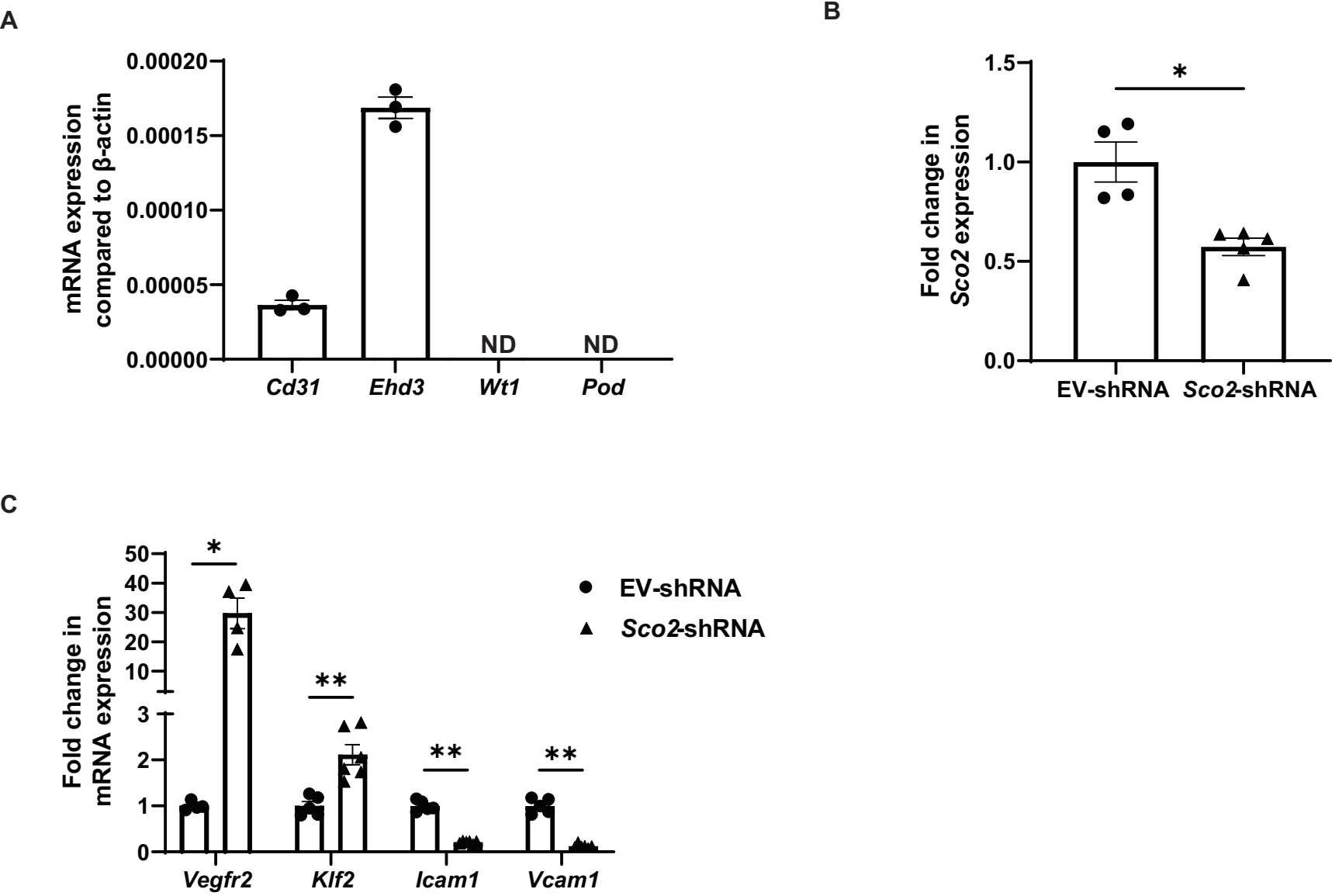

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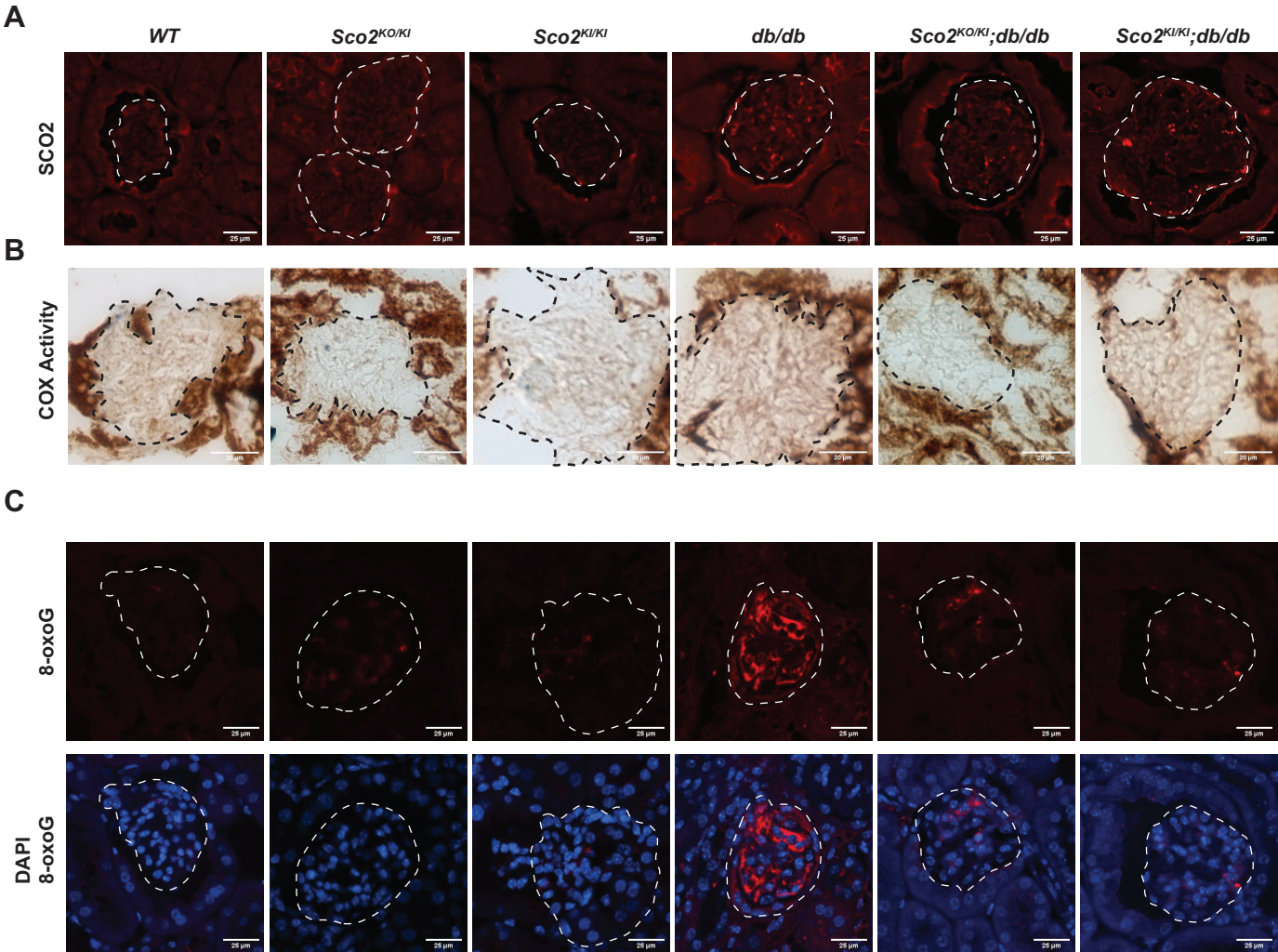

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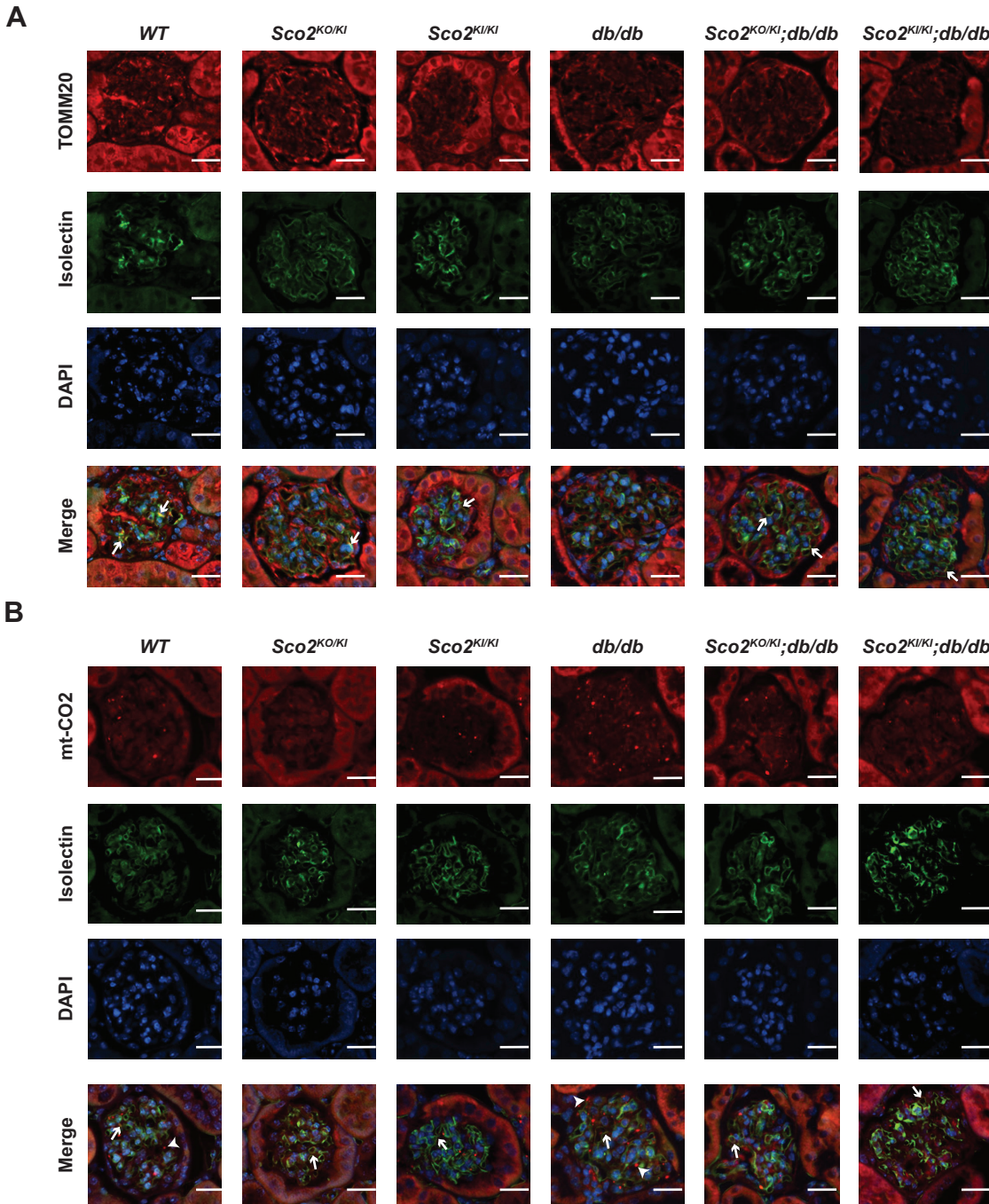

Supplementary Figure 11