

Single-cell and spatial transcriptomics reveals potential molecular mechanisms of *Abelmoschus manihot* (L.) Medic in treating diabetic kidney disease

Chenhua Wu^{1,2}, Haitao Tang³, Yihong Yu^{1,2}, Yuhui Song¹, Haitao Ge⁴, Yiming Shen², Jie Wu^{2*}, Harvest F. Gu^{1,5*}

1 Laboratory of Molecular Medicine, School of Basic Medicine and Clinical Pharmacy, China Pharmaceutical University, Nanjing, Jiangsu Province, China

2 Laboratory of Minigene Pharmacy, School of Life Science and Technology, China Pharmaceutical University, Nanjing, Jiangsu Province, China

3 Shandong Provincial Key Laboratory of Neuroimmune Interaction and Regulation; Department of Otorhinolaryngology, Head and Neck Surgery, Yantai Yuhuangding Hospital, Qingdao University; Shandong Provincial Clinical Research Center for Otorhinolaryngologic Diseases, Yantai 264000, China

4 College of Pharmacy, Chemistry and Chemical Engineering, Taizhou University, Taizhou, Jiangsu Province, China

5 School of Chinese Medicine, Nanjing University of Chinese Medicine, Nanjing, Jiangsu Province, China

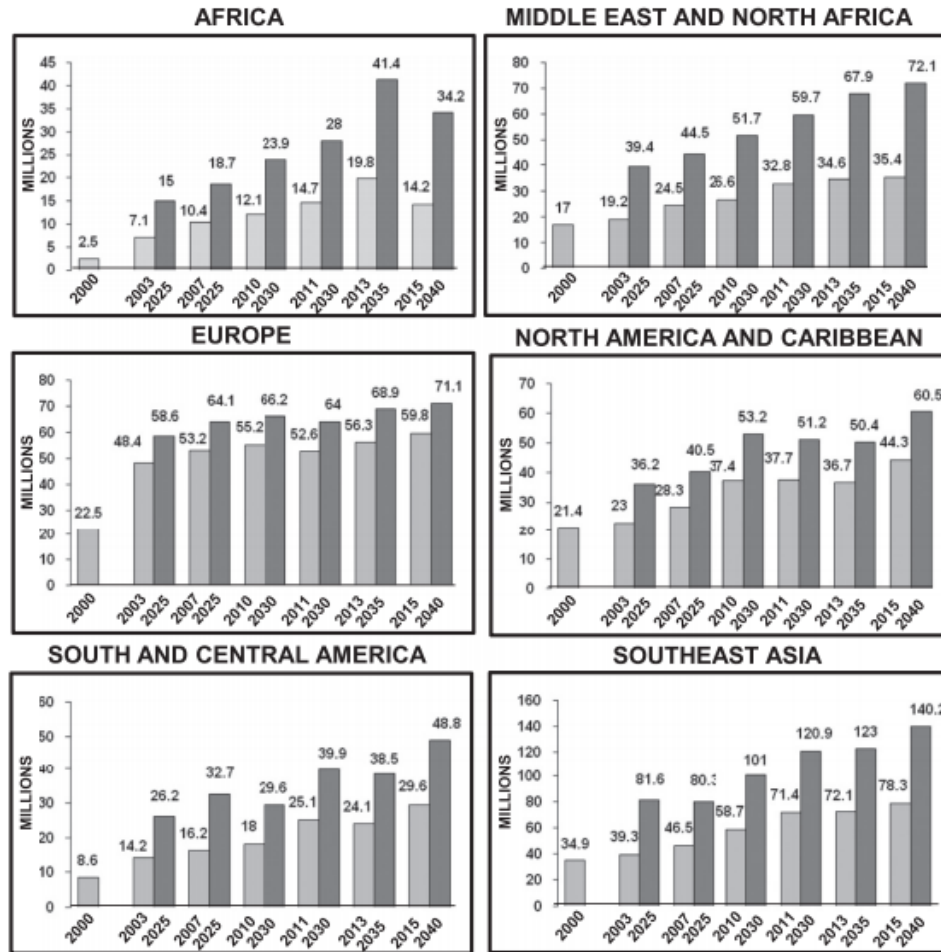
6 College of Pharmacy, Qilu Medical University, Zibo, Shandong Province, China



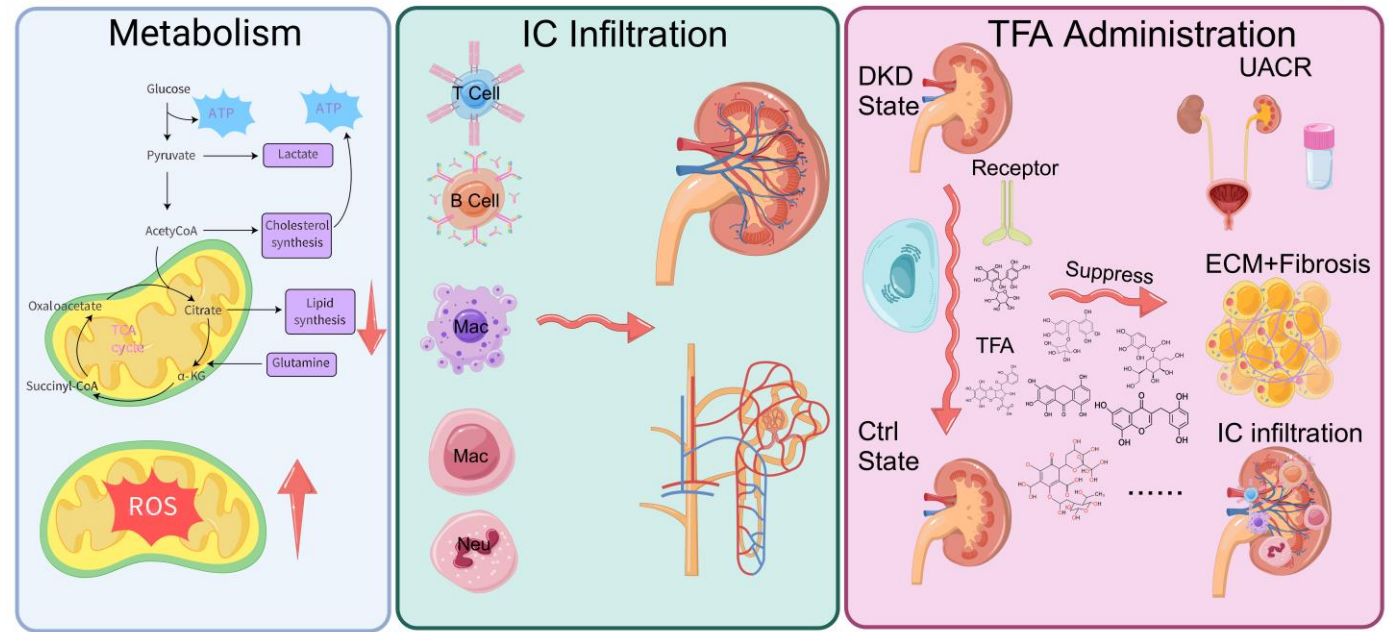
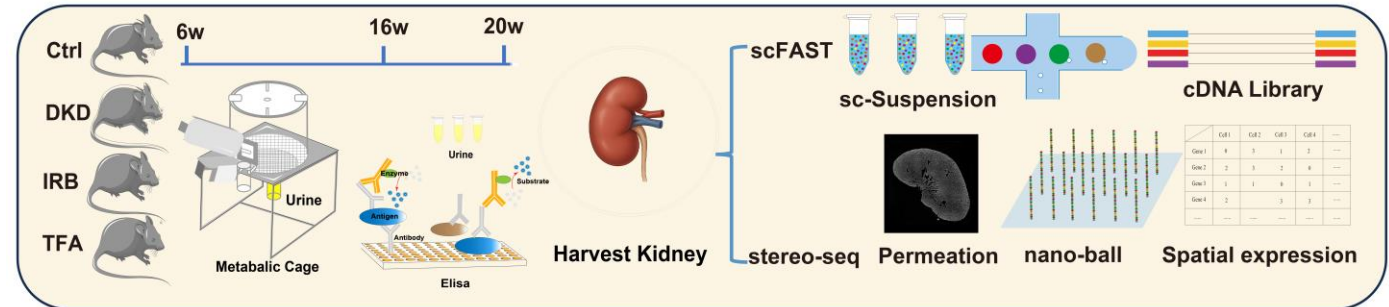
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Brief Introduction



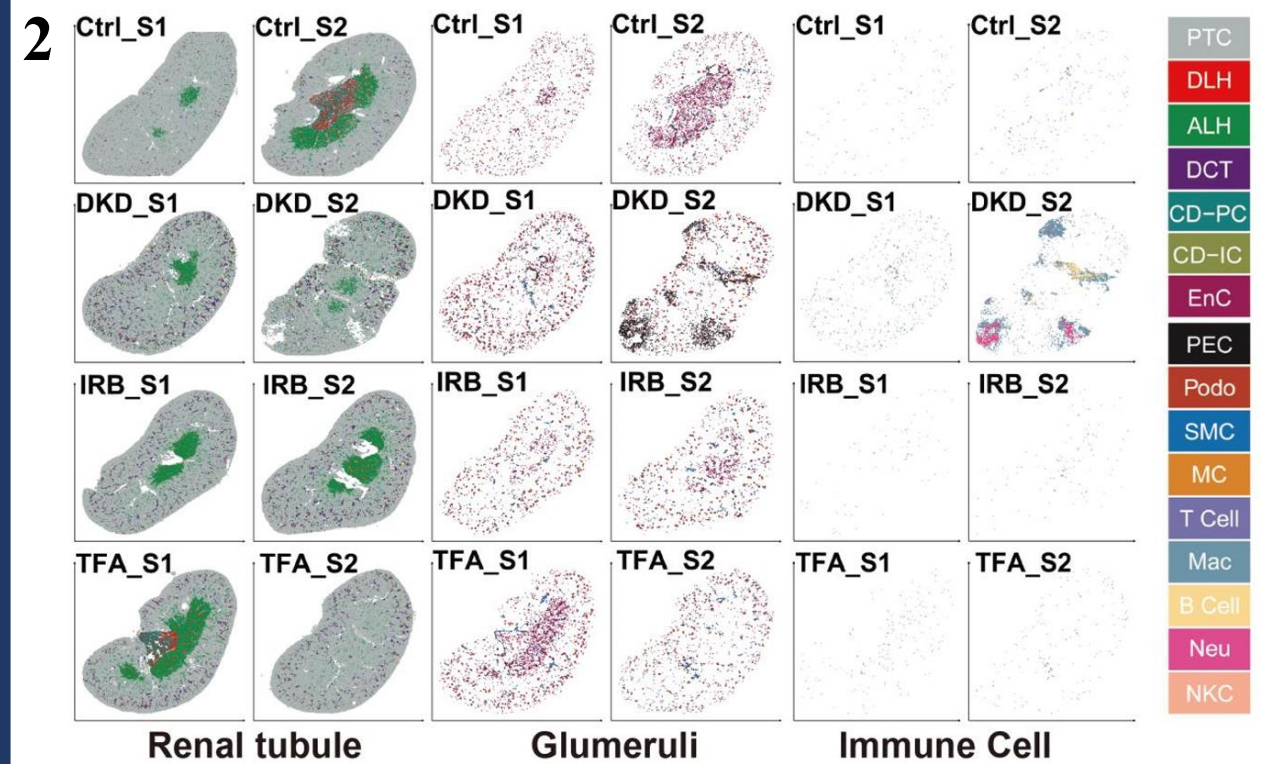
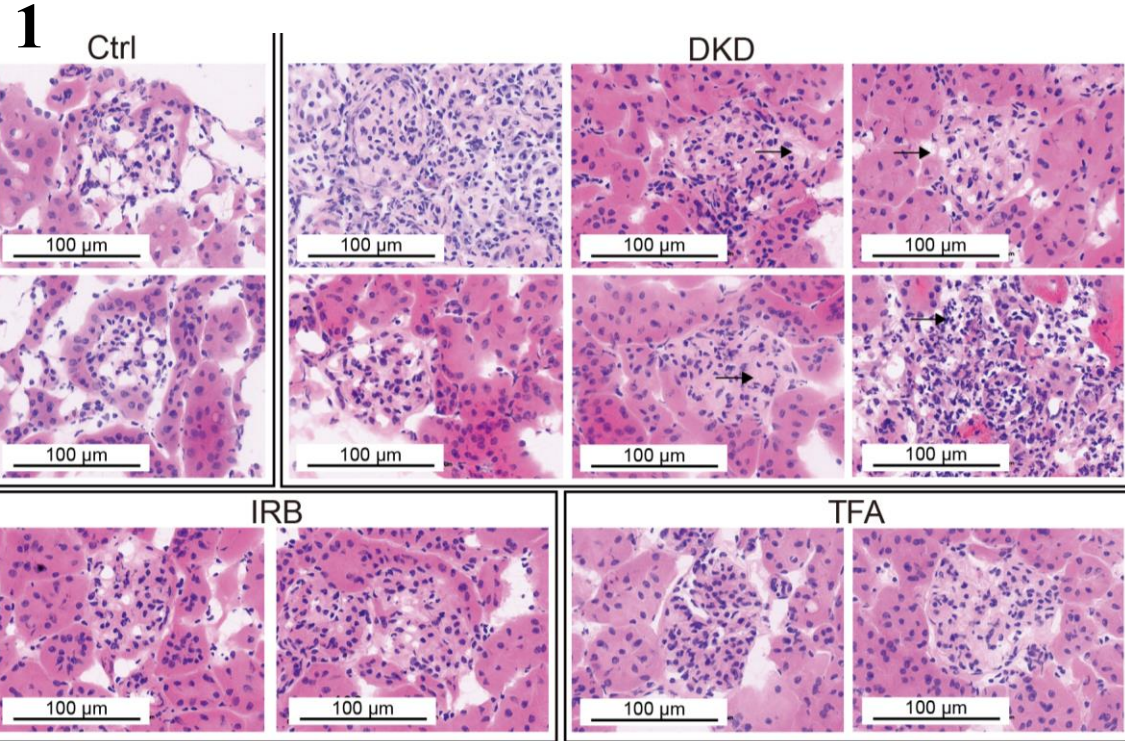
The global prevalence of type 2 diabetes and diabetic kidney disease (DKD) continues to increase, posing significant health and financial burdens on affected individuals. The pathogenesis and therapeutic mechanisms of DKD remain to be further elucidated.



Elucidating Mitochondrial Homeostasis, Immune Infiltration, and Therapeutic Mechanisms of Irbesartan and total Flavonoids of *Abelmoschus manihot* (TFA) in Diabetic Kidney Disease through Combined Spatial Transcriptomics and scRNA-seq – Nature Methods' 2020 Method of the Year.



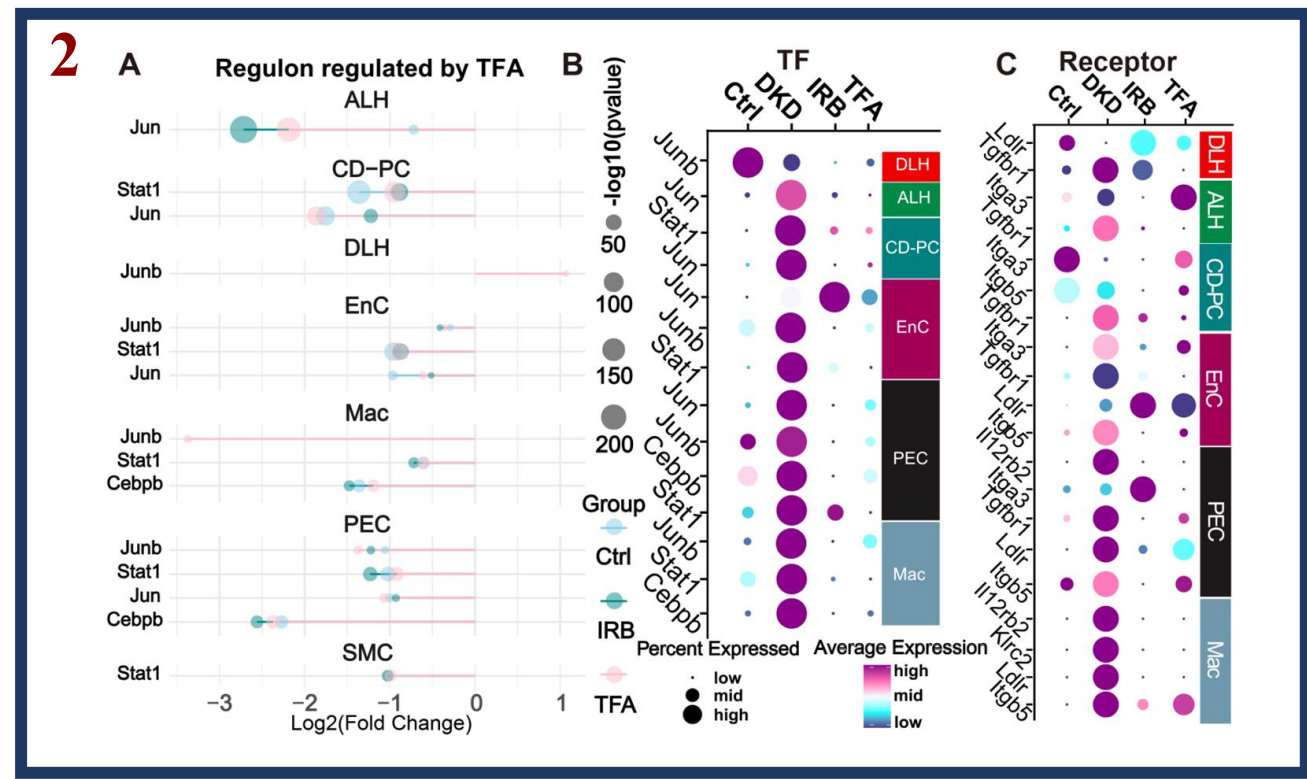
Results-Sptial Transcriptional Profile



1 TFA was demonstrated to alleviate classic pathological features of DKD, including glomerulosclerosis, mesangial matrix expansion, collagen deposition, Kimmelstiel-Wilson nodules, glomerular basement membrane thickening, and excessive inflammatory cell infiltration.

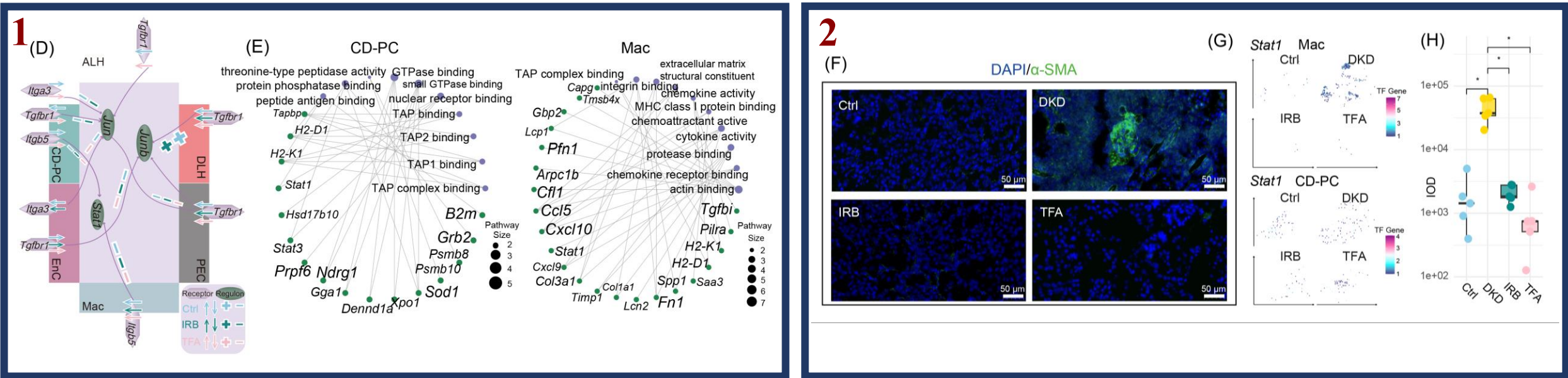
2 A spatial transcriptome encompassing 16 cell types across three tissue components (renal tubules, glomeruli, and immune cells) was initially obtained.

1



The ligand→receptor→TF→TG regulatory network HKC in treating DKD, which we previously published in Phytomedicine, was recapitulated in the spatial transcriptomic data. Similar to HKC, TFA alleviates DKD by regulating receptors including *Tgfbr1*, *Itgb5*, and *Itga3*, acting on TF *Junb*, *Jun*, and *Stat1*, and modulating pathways such as immune infiltration and fibrosis.


Result - Therapeutic Mechanism of *Abelmoschus manihot*








In CD-PC, EnC, Mac, PEC, and SMC, both the *Stat1* regulon and its corresponding gene expression were negatively regulated by IRB and TFA. Spatial analysis results demonstrated that the transcription factor *Stat1* specifically exhibited a dense, high-intensity expression pattern in CD-PC of DKD samples and colocalized with immune cells, whereas the expression intensity was low in other groups. Functional enrichment analysis of the top 50 most strongly co-expressed target genes in the *Stat1* regulon revealed that: in CD-PC, the target genes of the *Stat1* regulon were mainly enriched in pathways related to peptide antigen binding, TAP binding, and TAP complex binding; while in Mac, the target genes of this regulon were enriched in pathways such as integrin binding, chemokine activity, and cytokine activity. The trend of immunofluorescence staining was consistent with the gene expression profile.



Interactive Website

 **Spatial Transcriptomics - DKD**

 Introduction  Spatial Plot  DotPlot  Pathway DotPlot  Sample Metadata

Welcome to explore!

This site provides an interactive spatial transcriptomics dataset related to DKD, enabling visualization of spatial distribution of cell types, gene expression levels, pathway activity scores, and metadata queries.


Study Description

In the current study, we administered 75.5 mg/kg body weight of TFA (TFA Group), 20.0 mg/kg body weight of IRB (IRB Group), or an equivalent volume of water (DKD Group) via gavage to BKS.Cg-Dock7m +/+ Leprdb/J (db/db) mice for a period of four weeks, with db/m mice serving as healthy controls. The progression of diabetic kidney disease (DKD) and the therapeutic effects of the treatment groups on renal function were assessed by collecting urine samples using metabolic cages and measuring the urinary albumin-to-creatinine ratio (UACR) via ELISA.

Summary

Utilizing a combination of single-cell full-length RNA sequencing (scFAST) and subcellular-resolution SpaTial Enhanced REsolution Omics-sequencing (stereo-seq) (A), we obtained a comprehensive dataset encompassing 16 distinct cell types, including proximal tubule cells (PTC), descending loop of Henle (DLH), ascending loop of Henle (ALH), distal convoluted tubule (DCT), connecting tubule principal cells (CD-PC), collecting duct intercalated cells (CD-IC), endothelial cells (EnC), parietal epithelial cells (PEC), podocytes (Podo), smooth muscle cells (SMC), mesangial cells (MC), T cells, macrophages (Mac), B cells, Neutrophil (Neu), and natural killer cells (NKC) (B). We have confirmed the biological identity of these cells through the canonical cell marker. RT included PTC (Kap, Pck1, 1,020,959), DLH (Cryab, Aqp1, 7,394), ALH (Slc12a1, Umod, 101,460), DCT (Slc12a3, Pvalb, 38,735), CD-PC (Aqp2, Fxyd4, 19,925), and CD-IC (Atp6v1g3, S100a1, 18,749). Glomerular cells included EnC (Flt1, Ptprb, 13,359), PEC (H2-K1, C3, 4,971), Podo (Nphs2, Pdoxl, 12,676), SMC (Acta2, Myl9, 6,172) and MC (Ccar1, Nr3c1, 9). IC include T Cell (Cd3g, Cd3e, 129), Mac (Lyz2, C1qb, 6,804), B Cell (Slpi, Iglv1, 1,409), Neu (S100a8, S100a9, 1,569), and NKC (Il2rb, Klrk1, 43). (C)

Graphic Summary



A

Ctrl 6w 16w 20w

DKD

Urine

scFAST

sc-Suspension

cDNA Library

	Cd11	Cd21	Cd31	Cd44	...
Gene1	0	1	1	2	---
Gene2	2	1	2	0	---

http://biomamba.com:34038/DKD_ST_dataset/



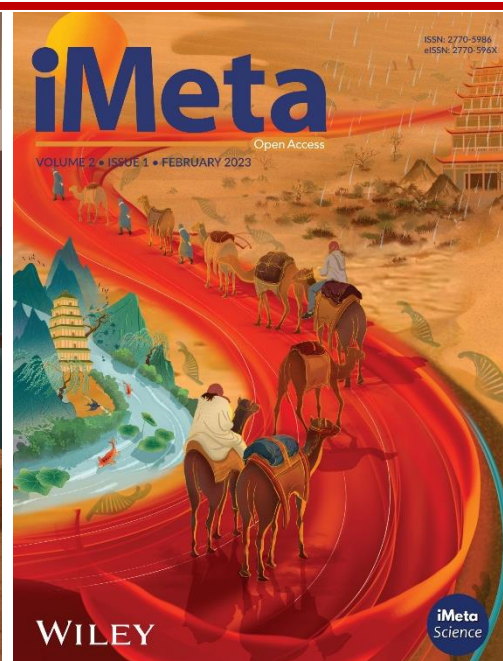
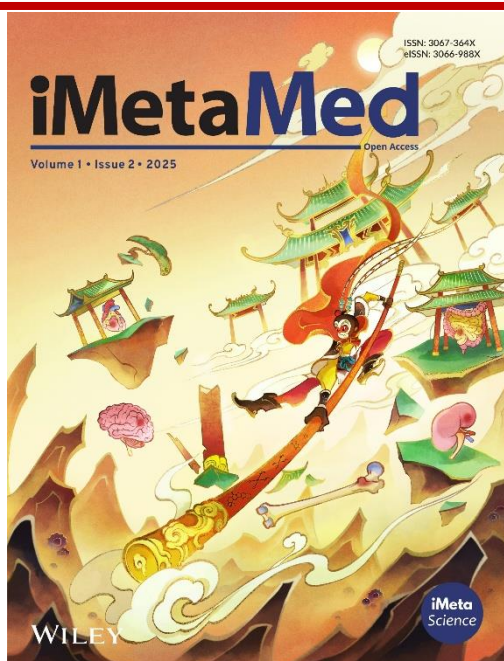
Summary

- 1. TFA exerts a therapeutic effect on the pathological progression of DKD comparable to that of IRB.**
- 2. Both TFA and IRB can effectively reduce the level of immune cell infiltration in DKD mice.**
- 3. Seven major flavonoid components in TFA can inhibit the *Tgfbr1* pathway and *Itgb5-Stat1* pathway to treat DKD.**
- 4. We welcome researchers to access the DKD-related pathways of interest through our online website.**

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