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

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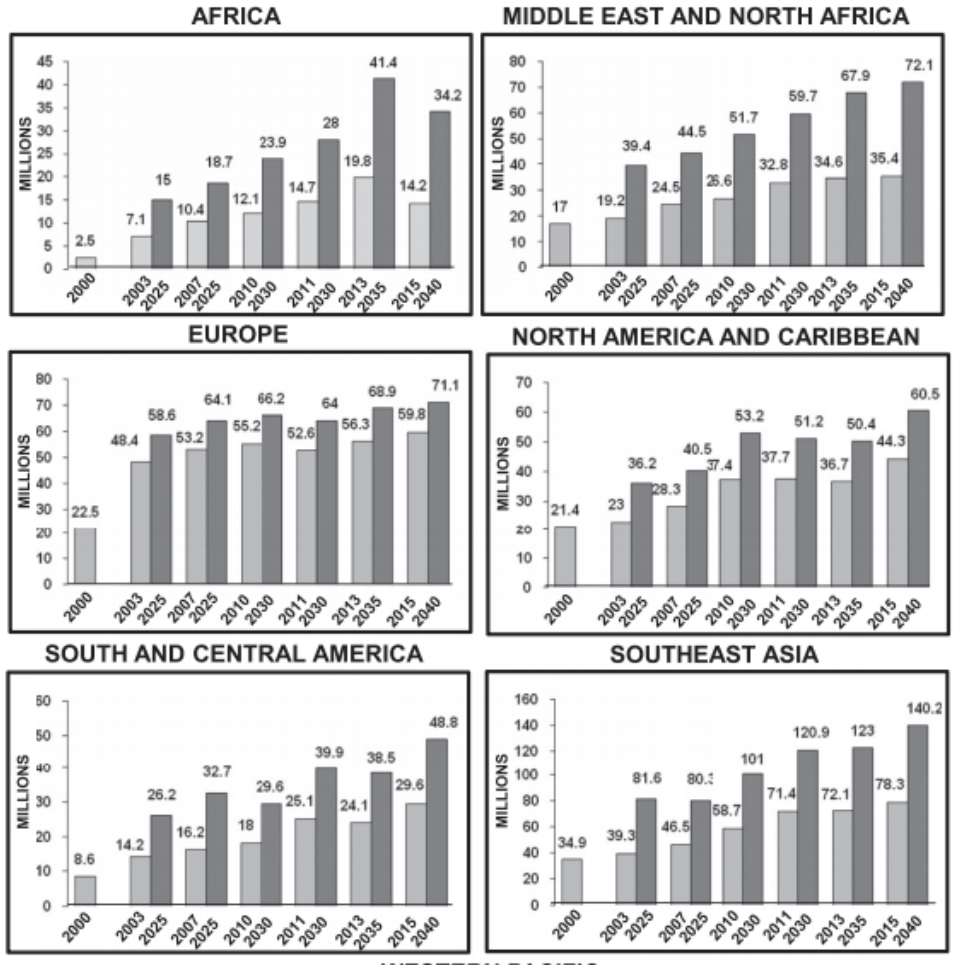
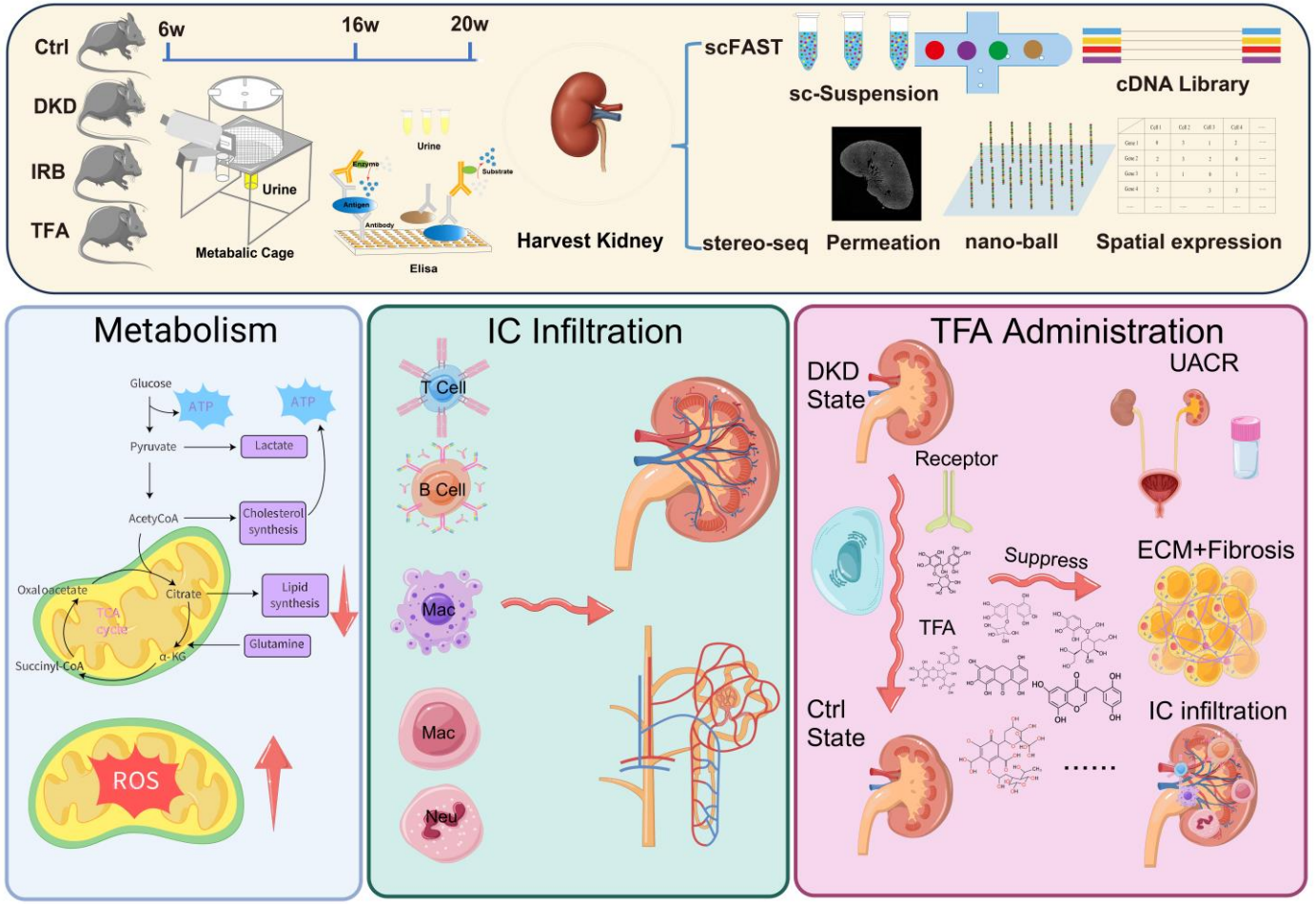
Brief Introduction

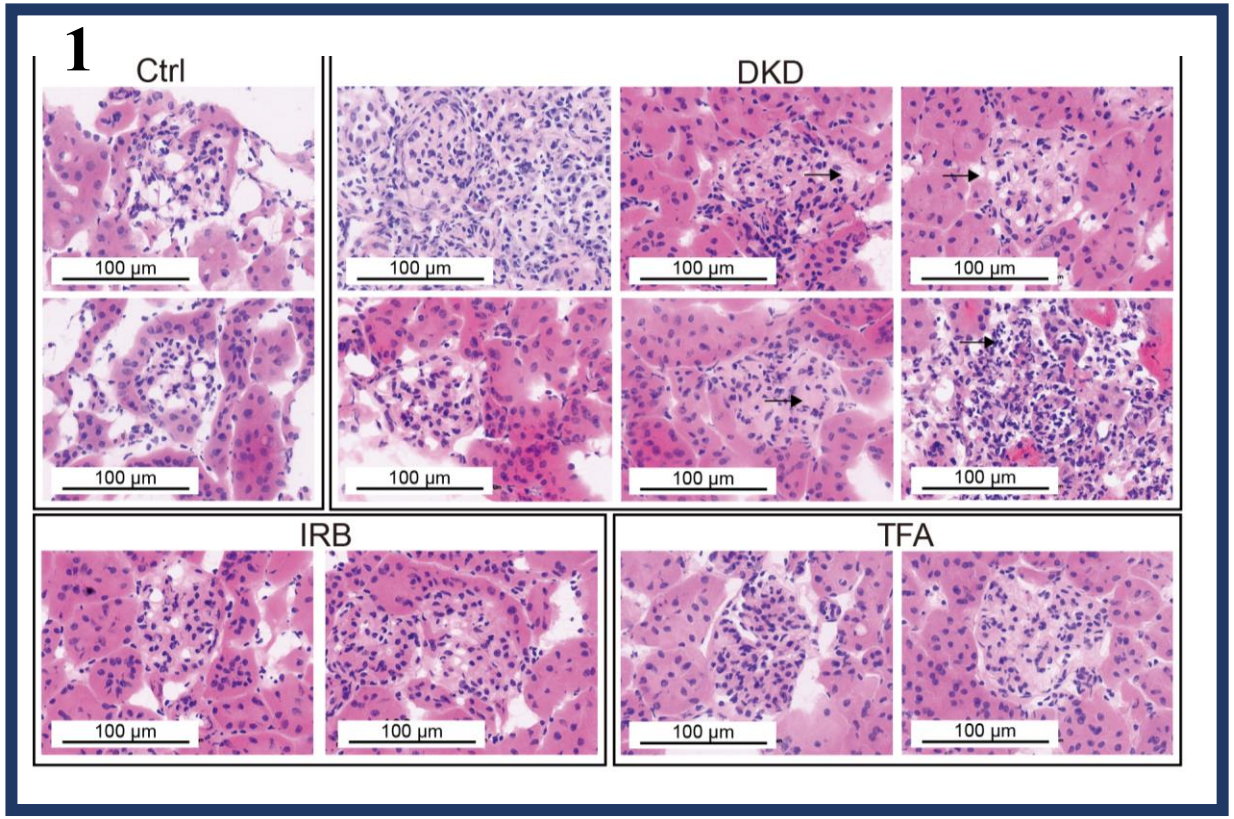


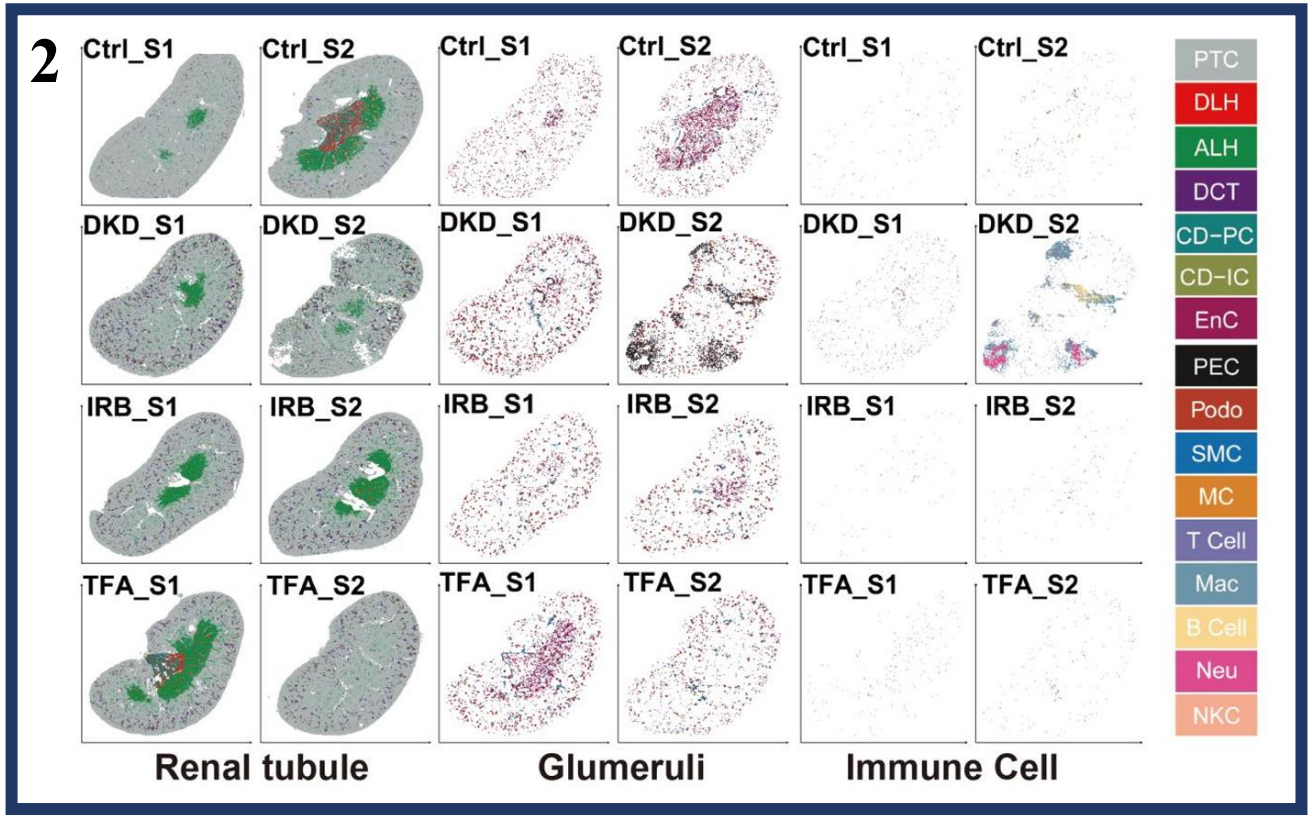
The global prevalence of type 2 diabetes and diabetic kidney disease (DKD) continues to increase, posing significant health and financial burdens on affected individuals. The pathogenesis and therapeutic mechanisms of DKD remain to be further elucidated.



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

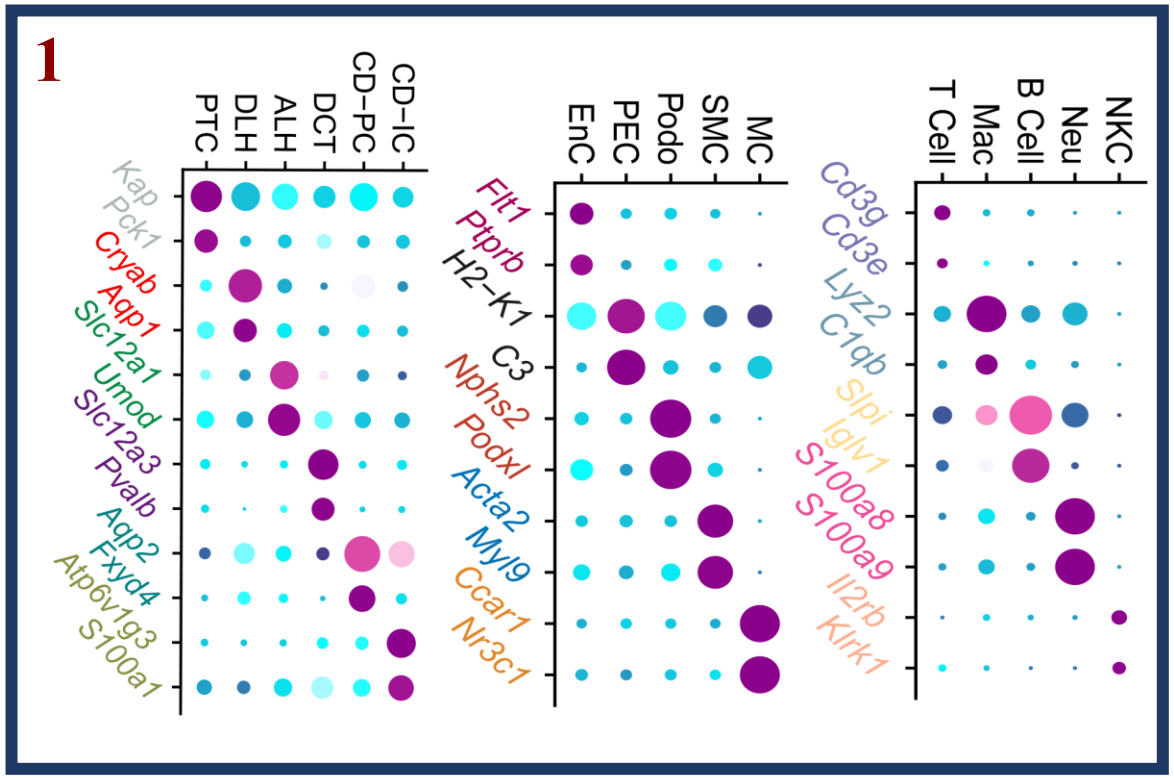


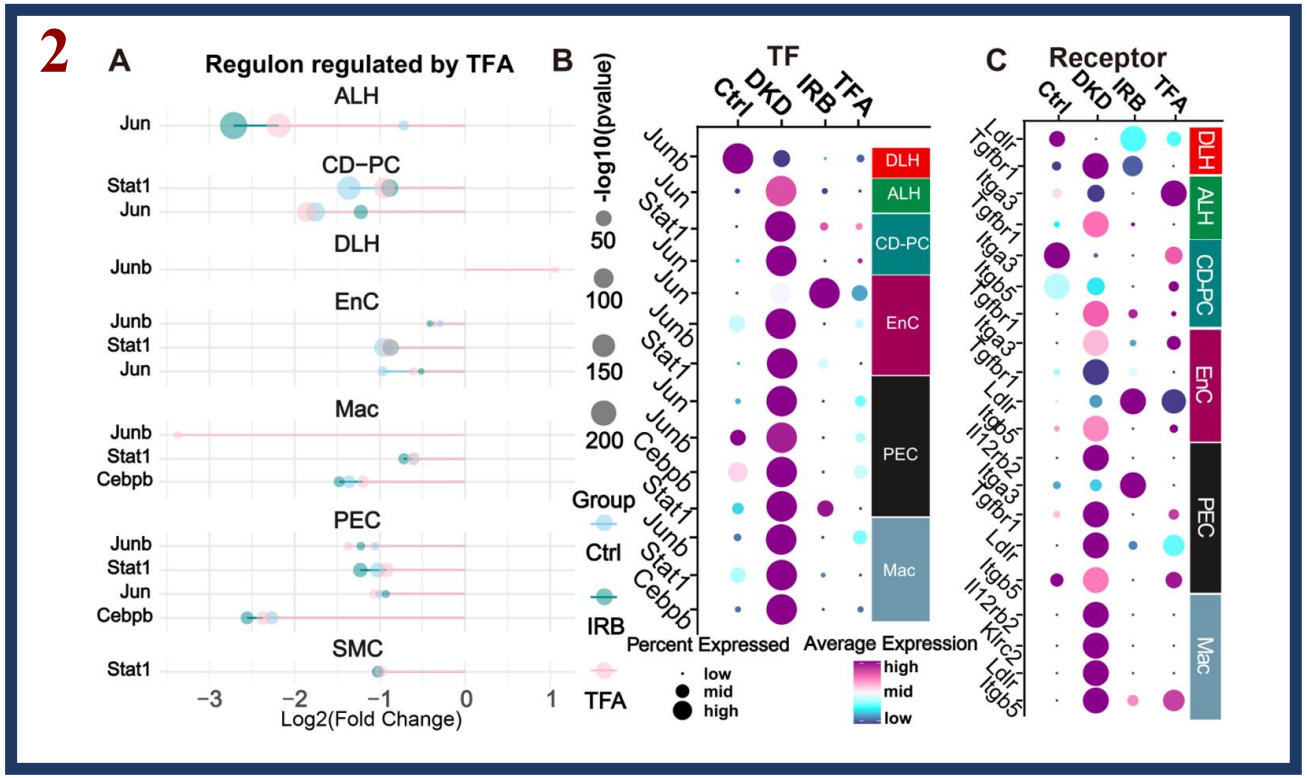


1 TFA was demonstrated to alleviate classic pathological features of DKD, including glomerulosclerosis, mesangial matrix expansion, collagen deposition, Kimmelstiel-Wilson nodules, glomerular basement membrane thickening, and excessive inflammatory cell infiltration.

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

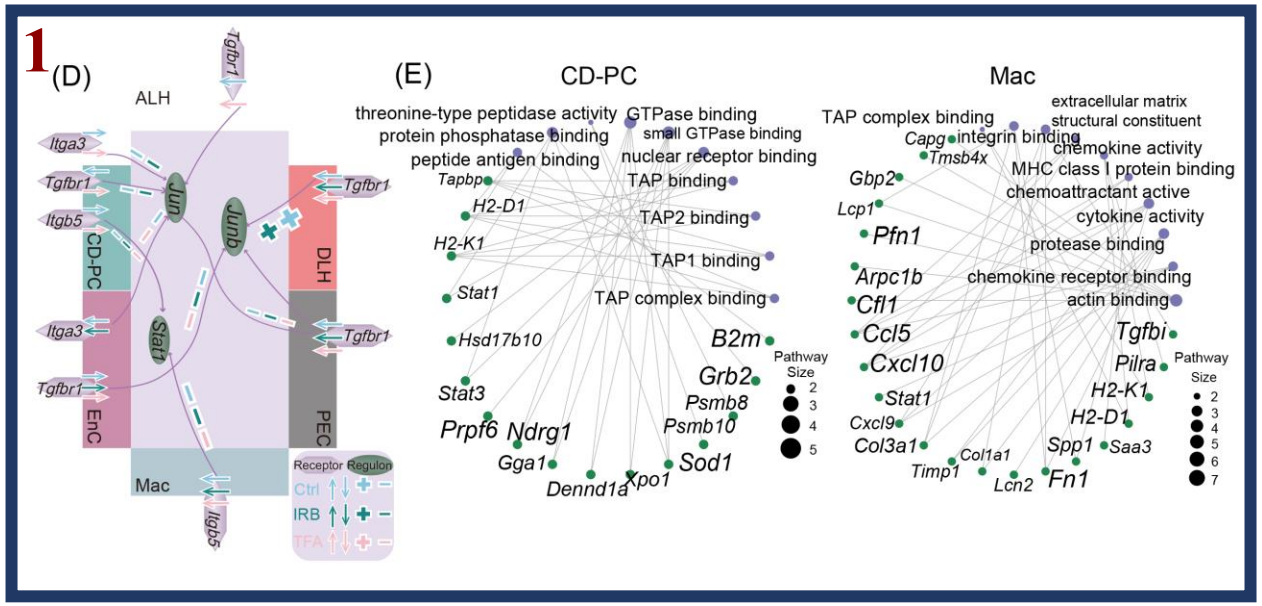
Result - Therapeutic Mechanism of *Abelmoschus manihot*

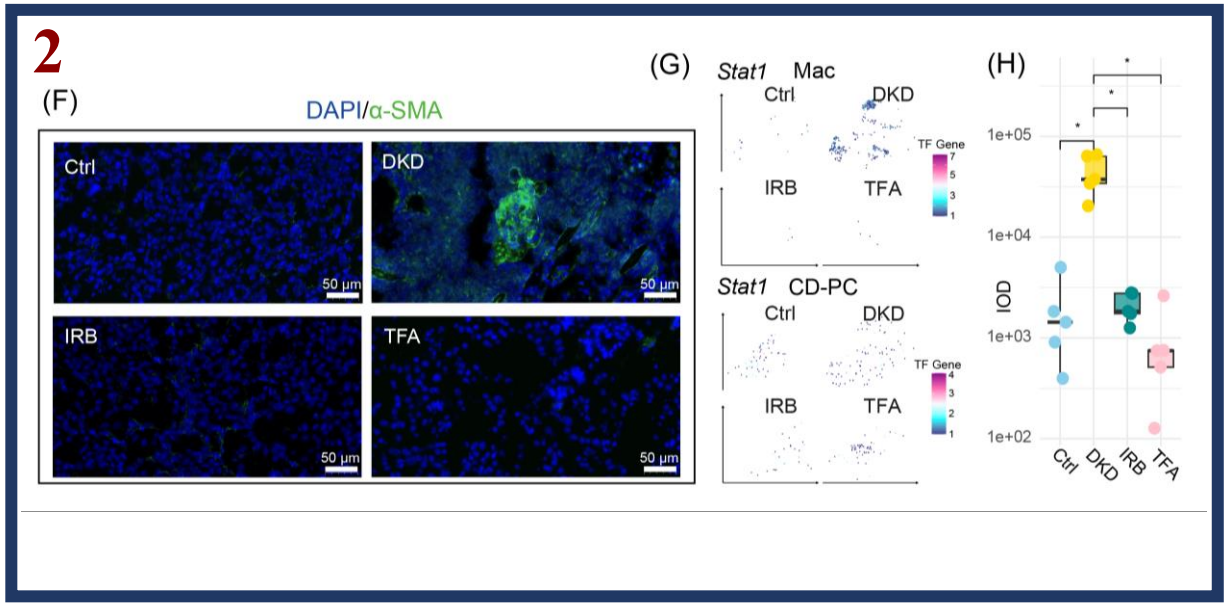




The ligand→receptor→TF→TG regulatory network HKC in treating DKD, which we previously published in Phytomedicine, was recapitulated in the spatial transcriptomic data. Similar to HKC, TFA alleviates DKD by regulating receptors including *Tgfbr1*, *Itgb5*, and *Itga3*, acting on TF *Junb*, *Jun*, and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

Result - Therapeutic Mechanism of *Abelmoschus manihot*

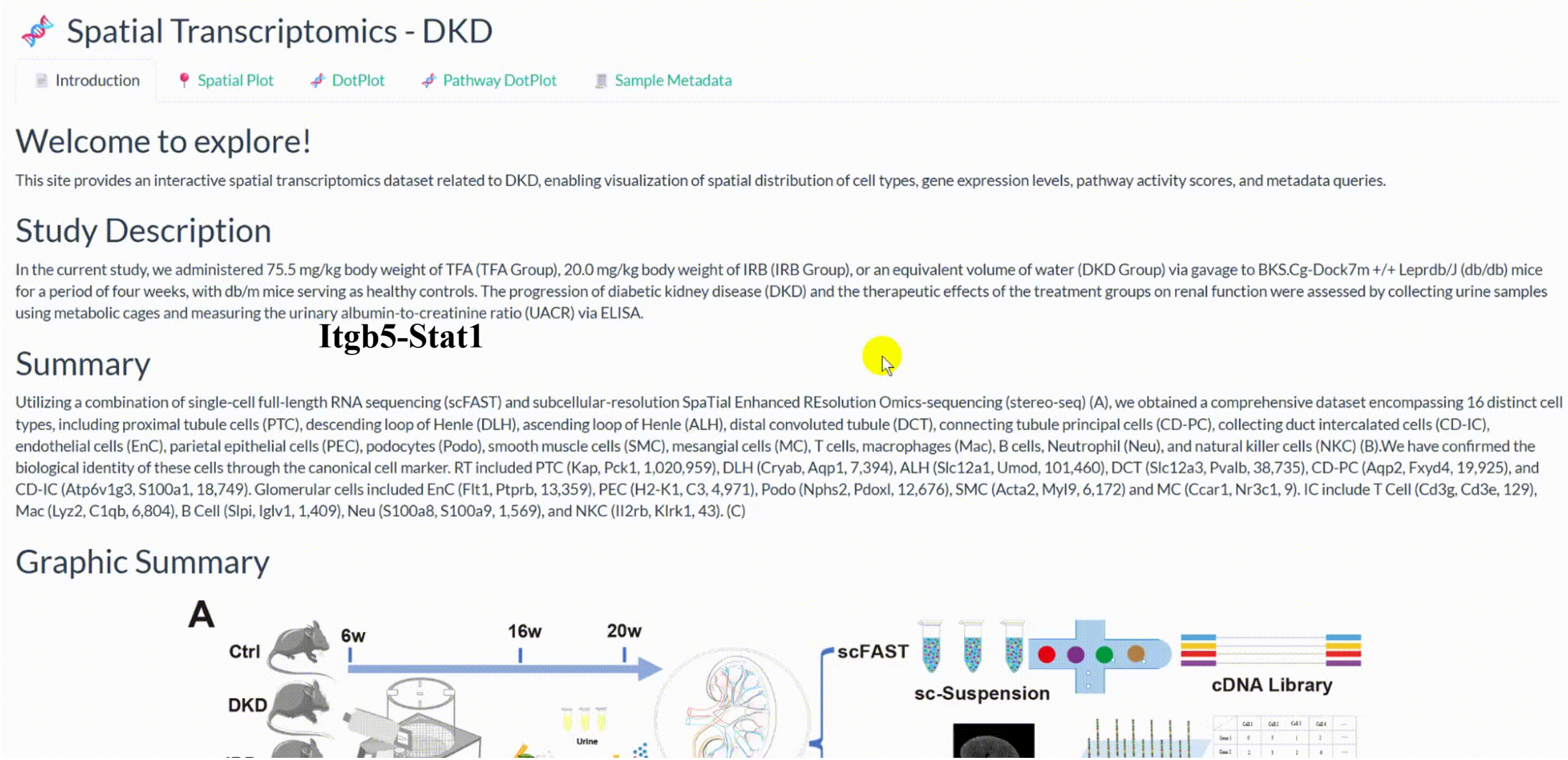




In CD-PC, EnC, Mac, PEC, and SMC, both the *Stat1* regulon and its corresponding gene expression were negatively regulated by IRB and TFA. Spatial analysis results demonstrated that the transcription factor *Stat1* specifically exhibited a dense, high-intensity expression pattern in CD-PC of DKD samples 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.

Academic sharing

Interative Website



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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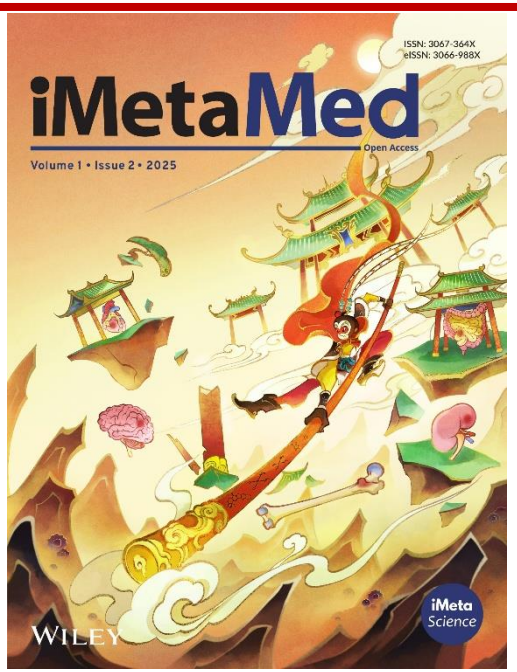

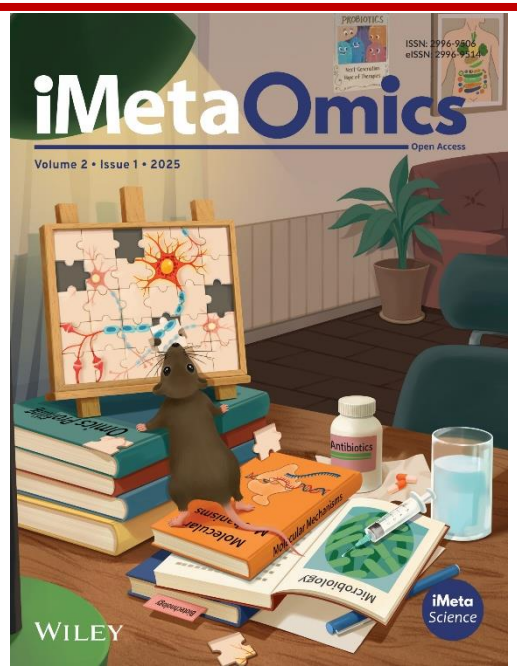

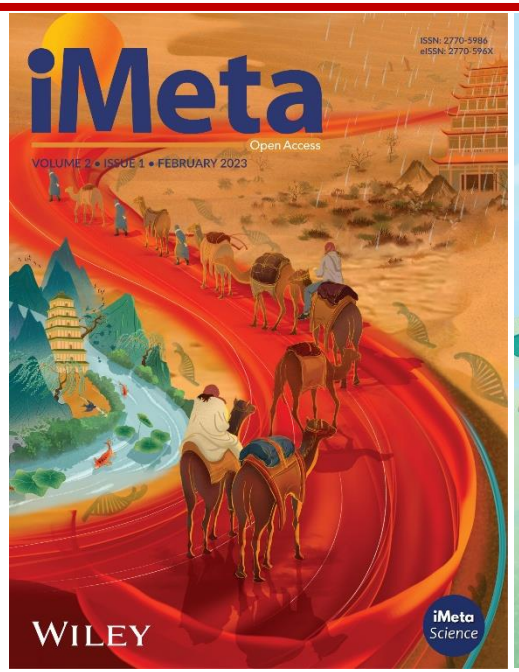

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