SLC6A19 inhibition drives a protective proximal-tubule metabolic state complementary to SGLT2 inhibition

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Introduction

SLC6A19 (B0AT1) is a sodium-coupled neutral amino acid transporter expressed on the apical membrane of renal proximal tubule cells, where it mediates the reabsorption of filtered neutral amino acids. Human predicted loss-of-function variants in SLC6A19 are associated with improved kidney function and a reduced risk of CKD progression, nominating SLC6A19 as a potential kidney-protective target. However, the renal effects and molecular mechanisms of pharmacologic SLC6A19 inhibition—and how they compare with SGLT2 inhibition—remain incompletely defined. Here, we evaluated the SLC6A19 inhibitor MZ-402 in an aristolochic acid I (AAI)-induced kidney injury model using kidney single-nucleus RNA sequencing to define treatment-associated changes in renal pathways and proximal tubule cell states. We also characterized the baseline transcriptional responses to 30 mg/kg and 100 mg/kg MZ-402 and compared them with dapagliflozin alone and in combination with 30 mg/kg MZ-402. Finally, spatially resolved proteomics of laser-capture microdissected proximal tubule S1 (PT-S1) and S3 (PT-S3) segments from *Slc6a19* knockout mice, with or without dapagliflozin treatment, was performed to assess segment-specific protein changes and distinguish SLC6A19- from SGLT2-associated molecular responses.

SLC6A19 inhibition is kidney protective

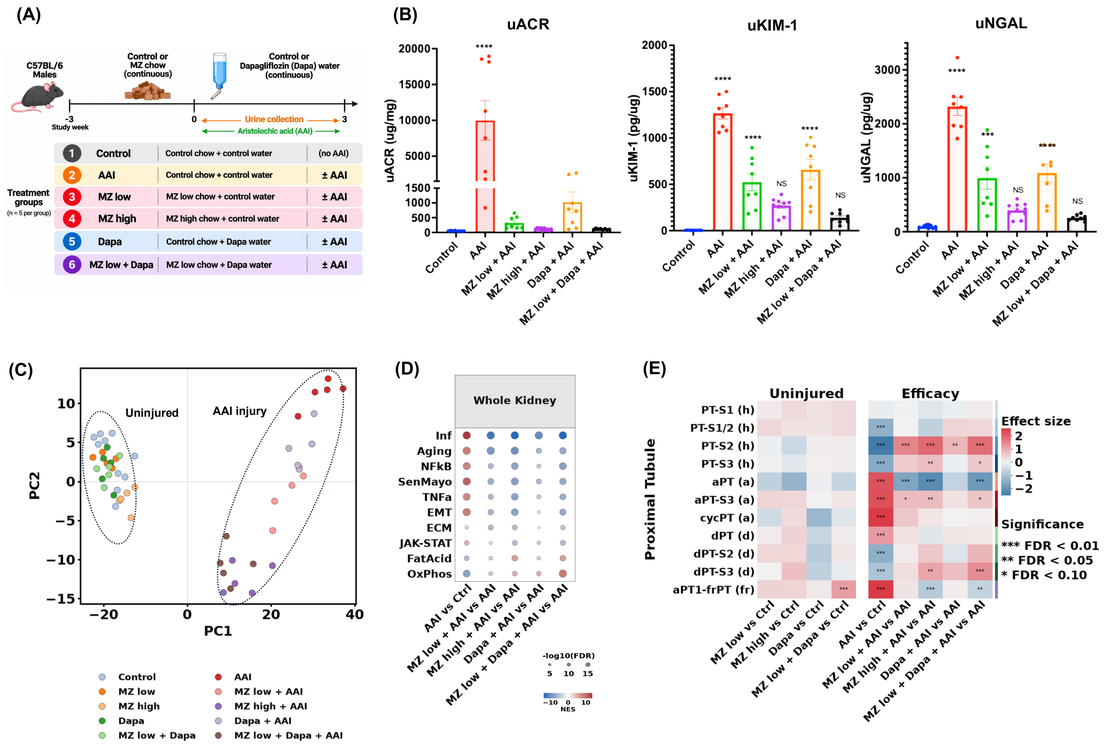

Figure 1. (A) Study design. Male C57BL/6 mice received control or MZ-402 chow and control or dapagliflozin (Dapa) drinking water for 6 weeks. AAI was administered during weeks 0–3, with urine collection during the injury phase (n = 5/group). MZ low = 30 mg/kg MZ-402; MZ high = 100 mg/kg MZ-402. **(B)** Kidney injury biomarkers. Urinary albumin-to-creatinine ratio (uACR), KIM-1, and NGAL demonstrate attenuation of selected AAI-induced injury markers by MZ-402, Dapa, and combination treatment. **(C)** Whole-kidney snRNA-seq. Principal component analysis (PCA) separates uninjured and AAI-injured kidneys, revealing treatment-dependent transcriptional changes. **(D)** Pathway analysis. Whole-kidney enrichment reveals modulation of AAI-associated inflammatory, stress, extracellular matrix, and metabolic pathways. Dot size indicates significance; color represents enrichment direction. **(E)** PT cell-state responses. Treatment-dependent changes in healthy, adaptive, and degenerative/failed-repair proximal tubule (PT) states across uninjured and AAI conditions. Color indicates effect size; asterisks denote FDR significance. **PT cell states:** PT-S1/S2/S3, healthy segment states; aPT, adaptive/injury-response PT; aPT-S3, adaptive S3-like PT; cyPT, cycling PT; dPT, degenerative PT; aPT1-frPT, adaptive/failed-repair PT.

SLC6A19 biology is distinct from SGLT2 inhibition

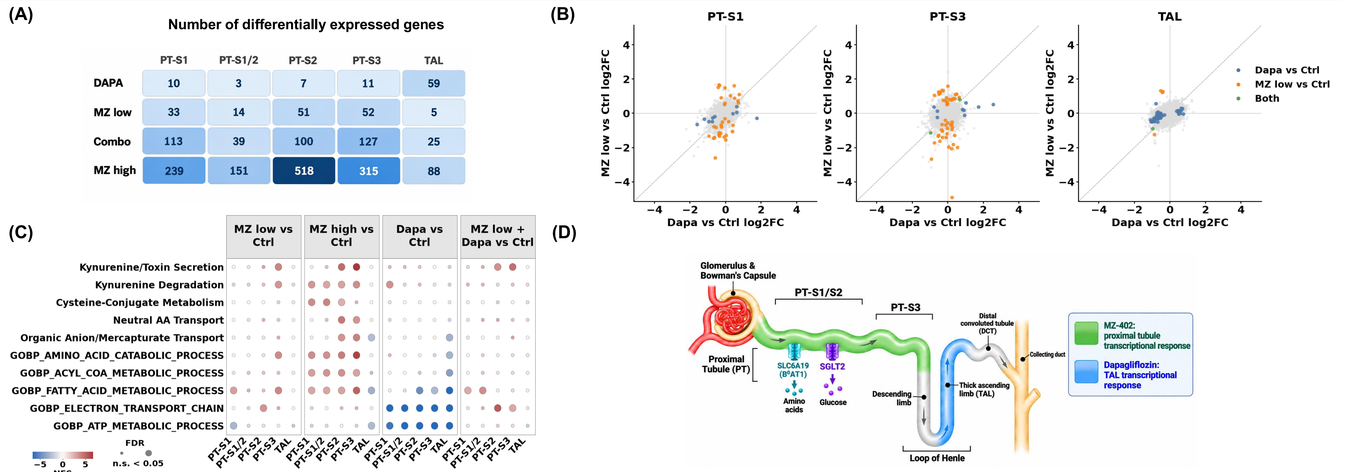

Figure 2. (A) Number of differentially expressed genes (DEGs) across nephron segments following MZ-402, dapagliflozin (Dapa), or combination treatment under uninjured conditions, highlighting a dose-dependent, PT-predominant MZ-402 response. **(B)** Correlation of gene $\log_2$ fold changes induced by MZ low and Dapa versus control in PT-S1, PT-S3, and TAL. Colored points indicate DEGs specific to either treatment or shared by both. **(C)** Pathway enrichment reveals MZ-402–associated changes in PT amino acid transport, kynurenine/uremic toxin handling, detoxification, and fatty acid metabolism, compared with Dapa-associated metabolic and electron transport chain responses. Dot size indicates significance; color represents enrichment direction. **(D)** Nephron schematic highlighting predominantly PT-associated transcriptional responses to MZ-402 and greater downstream/TAL involvement with Dapa.

Proteomics distinguishes SLC6A19 and SGLT2 kidney responses

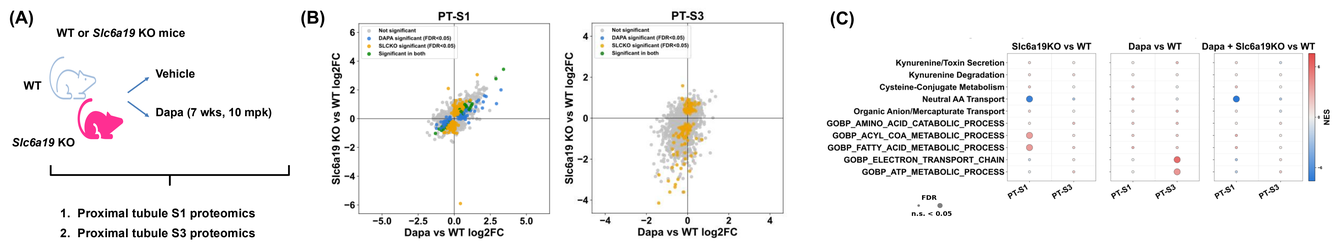

Figure 3. (A) WT and *Slc6a19* knockout (Slc6a19KO) mice received vehicle or dapagliflozin (Dapa; 10 mg/kg) for 7 weeks; laser-captured PT-S1 and PT-S3 segments were analyzed by spatial proteomics. **(B)** Protein-level correlations comparing Dapa and Slc6a19KO versus WT show limited overlap and segment-specific responses (FDR < 0.05). **(C)** Selected proteins linked to snRNA-seq pathways support Slc6a19KO-associated amino acid/metabolic remodeling and Dapa-associated mitochondrial and nutrient-transport remodeling in PT-S1 and PT-S3.

Conclusions

- SLC6A19 inhibition protects against AAI-induced kidney injury, preserving healthier proximal-tubule states and attenuating inflammatory, senescence, JAK–STAT, EMT/ECM, and metabolic dysfunction signatures; effects strongest at high dose and in combination with dapagliflozin.
- SLC6A19 inhibition drives a distinct, proximal tubule–predominant transcriptional program involving amino acid and organic anion transport, kynurenine/uremic toxin handling, and oxidative/fatty acid metabolism, differentiating it from the dapagliflozin response.
- Kidney proteomics supports this differentiated biology, with SLCKO enriched for amino-acid transport/metabolic remodeling and dapagliflozin showing more mitochondrial metabolic changes.

SLC6A19 inhibition engages a distinct proximal tubule nephroprotective program that may complement SGLT2 inhibition. An investigational small molecule inhibitor of SLC6A19, MZE782, is currently being evaluated as a potential therapy for CKD.