Shared and Distinct Renal Transcriptome Signatures in Three Standard Mouse Models of CKD

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Background & Aim

Various mouse models with differing disease etiologies are available in preclinical chronic kidney disease (CKD) research. Characterizing these models according to their renal transcriptomics enables better selection of the optimal model for preclinical drug discovery studies. We therefore characterized the kidney transcriptome signature of three well-established models of CKD, i.e. adenine-supplemented diet feeding (ADI), unilateral ureter obstruction (UUO) and unilateral ischemic reperfusion injury (uIRI).

Methods

Male C57BL/6J mice were used in all studies. Mice underwent UUO or uIRI surgery and were terminated two- and six-weeks post-surgery, respectively. Sham-operated mice served as controls. For ADI, mice received an adenine-supplemented diet or control diet for six weeks. Endpoints included plasma biochemistry and RNA sequencing.

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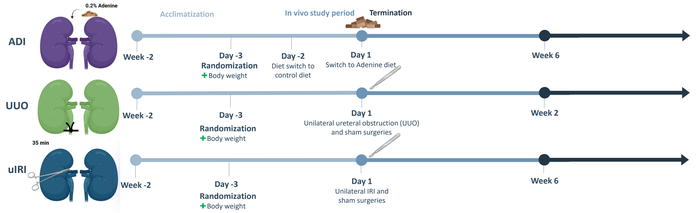
1 Model study design and physiological data



Group	Animals	Body weight (randomization) (g)	Body weight (term) (g)	Left kidney weight (mg)	Right kidney weight (mg)	Plasma Urea (mmol/L)
ADI control	8	27.6 ± 0.335	27.49 ± 0.562	167.5 ± 5.11	168.75 ± 5.05	7.9 ±0.368
ADI	8	27.6 ± 0.312	21.13 ± 0.493***	152.75 ± 5.92	145.25 ± 6.13**	25.6 ± 1.48 ***
UUO control	8	23.2 ± 0.438	23.6 ± 0.553	146.5 ± 4.27	154 ± 4.57	8.94 ± 0.449
UUO	8	23.2 ± 0.388	23.8 ± 0.524	148 ± 10.9	179 ± 5.98*	9.25 ± 0.666
uIRI control	10	22.9 ± 0.429	26.48 ± 0.609	156 ± 6.46	164 ± 6.53	9.98 ± 0.627
uIRI	10	24.2 ± 0.397	24.5 ± 0.389*	63.8 ± 4.1 ***	182.1 ± 5.76	10.74 ± 0.366

Figure 1. Study Design and Physiological Data for ADI, UUO, and uIRI Mouse Models. **(A)** Overview of the study design for ADI, UUO, and uIRI mouse models. **(B)** Physiological characteristics of the murine models. Values are presented as mean ± SEM. Statistical significance was determined using a two-tailed Dunnett's test, with *p<0.05, **p<0.01, ***p<0.001 compared to respective controls.

2 ADI, UUO and uIRI models exhibit large overlaps in transcriptomic signatures

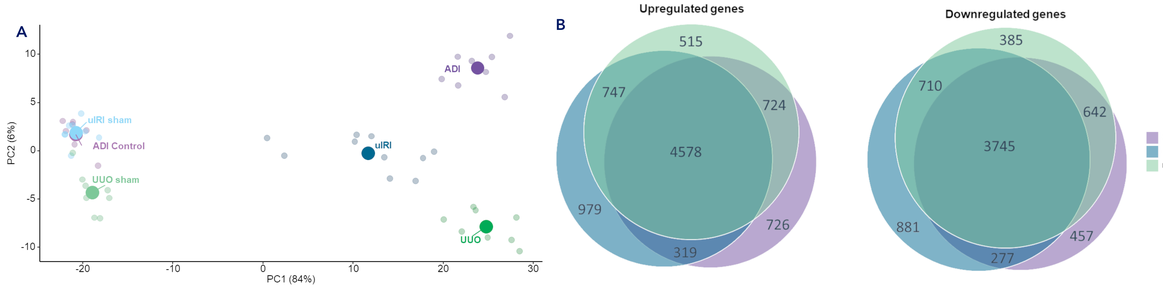


Figure 2. Transcriptomics Analysis Reveals Phenotypic Distinctions and Shared Transcriptome Signatures Among ADI, UUO, and uIRI Mice. **(A)** Principal Component Analysis (PCA) plot displaying gene expression changes in the top 500 most variable genes. Small dots represent individual samples, while large dots indicate the group's centroid. **(B)** Venn diagrams depicting the overlapping and distinct differentially expressed genes in ADI, uIRI and UUO models.

3 Transcriptomic signatures of pre-clinical and clinical drug targets

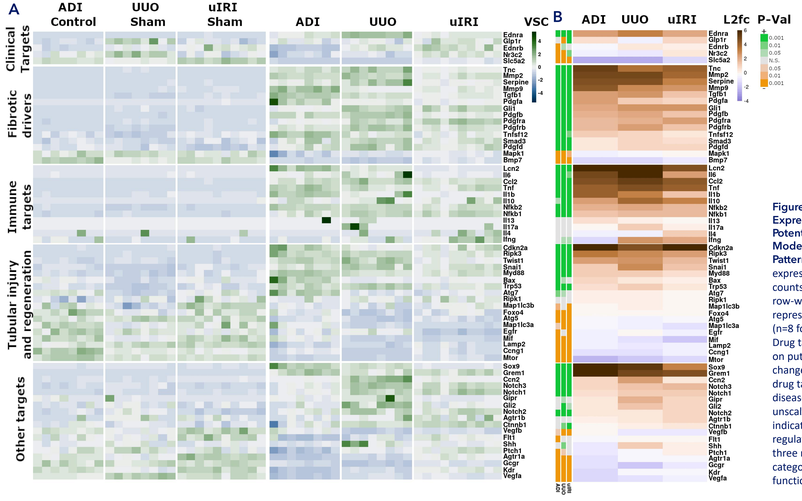


Figure 3. Analysis of Gene Expression in Current and Potential Drug Targets Reveals Model-Specific Regulatory Patterns. **(A)** Heatmap of gene expression (Variance corrected counts) of CKD drug targets, scaled row-wise, with squares representing individual animals (n=8 for ADI,UUO, n=10 for uIRI). Drug targets are categorized based on putative function. **(B)** Log2-fold change in gene expression of CKD drug targets from control to disease-model animals. Rows are unscaled. Additionally, p-values indicating the directionality of regulation are provided for all three models. Drug targets are categorized by their putative functions.

4 Expression signatures of Current clinical drug targets

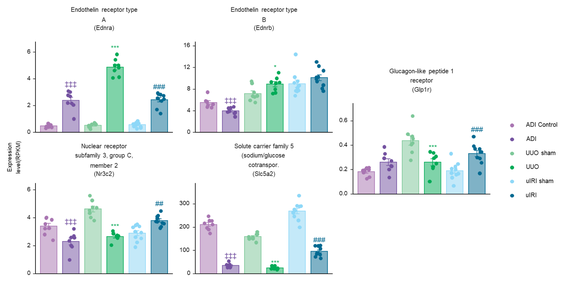


Figure 4. Current clinical targets reveal similarities and differences in regulation between models. Expression levels of current drug targets are shown as mean ± S.E.M RPKM values. *p<0.05, ***p<0.001 compared to UUO sham. ‡‡‡p<0.001 compared to ADI control. ##p<0.01, ‡‡‡p<0.001 compared to uIRI sham.

Conclusion

- The adenine-supplemented diet, unilateral ureter obstruction, and unilateral ischemic reperfusion injury mouse models displayed pronounced similarities in their transcriptomic signatures.
- Distinct transcriptomic signatures were observed in both current clinical and pre-clinical drug targets across the three models.
- These models exhibit different utility for pre-clinical research, emphasizing the importance of considering differences in transcriptomic signatures when designing experimental studies

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