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Compartment-Specific Adaptive Responses and Dysregulation Under NQO1 Deficiency in Diabetic Kidney Disease: A Transcriptomic GSEA-Based Investigation

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Objectives : Diabetic kidney disease (DKD) leads to oxidative stress-driven damage in glomeruli (Gloms) and proximal convoluted tubules (PCT). NAD(P)H quinone oxidoreductase 1 (NQO1) regulates redox balance, but its compartment-specific function in DKD remains unclear. We investigated how NQO1 deficiency affects glomerular and tubular adaptations under hyperglycemia.
Methods : STZ-induced diabetic NQO1-knockout (NKO) and wild-type (WT) mice were analyzed. Albuminuria, podocyte injury, and foot process effacement were assessed. To investigate the mechanisms, we conducted compartment-specific transcriptomic Gene Set Enrichment Analysis (GSEA) in glomeruli and PCT. Region of Interest (ROI) analysis was performed using histological markers (CD10, CD31, PanCK) to define glomerular and tubular regions for transcriptomic profiling. Gene Set Enrichment Analysis (GSEA) was conducted on differentially expressed genes ($P < 0.05$, q-value < 0.25) using KEGG gene sets to identify dysregulated pathways in NKO-STZ.
Results : NKO-STZ exhibited significantly higher albuminuria than WT-STZ ($P < 0.05$), indicating greater glomerular injury. Electron microscopy confirmed severe podocyte effacement and increased GBM thickness in NKO-STZ compared to WT-STZ. GSEA analysis revealed that in glomeruli, ribosome biogenesis and immune pathways were upregulated in WT-STZ compared to WT but suppressed in NKO-STZ compared to STZ, indicating impaired protein synthesis and immune regulation in NQO1 deficiency. In PCT, ribosome activity, oxidative phosphorylation, cytoskeletal, and other metabolic pathways were elevated in WT-STZ but suppressed in NKO-STZ, though ribosome activity was relatively less suppressed than in glomeruli. Additionally, adherens junction activation was more pronounced in WT-STZ glomeruli than in NKO, suggesting a compensatory mechanism to maintain podocyte foot process integrity. This response involved key cytoskeletal genes, including Actg1, Ctnna1, Tjp1, Rhoa, and Iqgap1.
Conclusions : These findings highlight compartment-specific adaptive responses to STZ-induced hyperglycemia and underscore NQO1's role in regulating these adaptations, suggesting it as a potential therapeutic target for mitigating DKD progression.

Figure1.png


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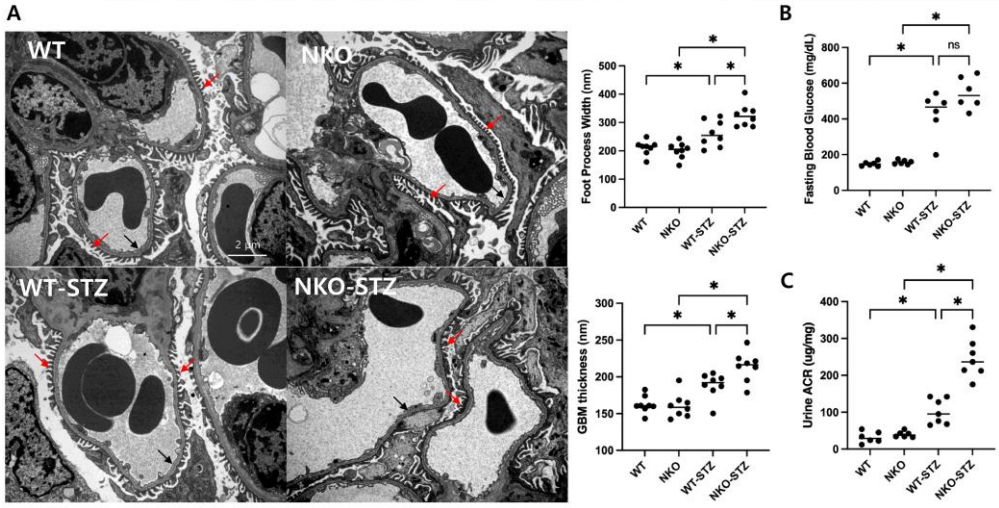
Beyond Challenges, Towards Healthier Kidney


A
WT
NKO
WT-STZ
NKO-STZ
2 μm
B
Foot Process Width (nm)
Fasting Blood Glucose (mg/dL)
GBM thickness (nm)
C
Urine ACR (ug/mg)
WT
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WT-STZ
NKO-STZ
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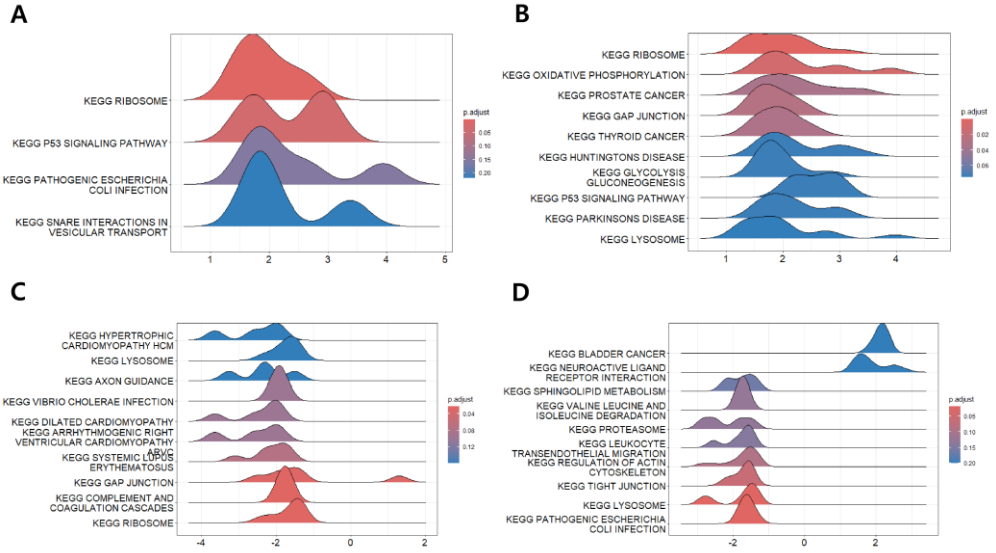
Figure1.png


A
KEGG RIBOSOME
KEGG P53 SIGNALING PATHWAY
KEGG PATHOGENIC ESCHERICHIA COLI INFECTION
KEGG SNARE INTERACTIONS IN VESICULAR TRANSPORT
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B
KEGG RIBOSOME
KEGG OXIDATIVE PHOSPHORYLATION
KEGG PROSTATE CANCER
KEGG GAP JUNCTION
KEGG THYROID CANCER
KEGG HUNTINGTONS DISEASE
KEGG GLYCOLYSIS GLUCONEOGENESIS
KEGG P53 SIGNALING PATHWAY
KEGG PARKINSONS DISEASE
KEGG LYSOSOME
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C
KEGG HYPERTROPHIC CARDIOMYOPATHY HCM
KEGG LYSOSOME
KEGG AXON GUIDANCE
KEGG VIBRIO CHOLERAE INFECTION
KEGG DILATED CARDIOMYOPATHY
KEGG ARRHYTHMOGENIC RIGHT VENTRICULAR CARDIOMYOPATHY ARVC
KEGG SYSTEMIC LUPUS ERYTHEMATOSUS
KEGG GAP JUNCTION
KEGG COMPLEMENT AND COAGULATION CASCADES
KEGG RIBOSOME
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D
KEGG BLADDER CANCER
KEGG NEUROACTIVE LIGAND RECEPTOR INTERACTION
KEGG SPHINGOLIPID METABOLISM
KEGG VALINE LEUCINE AND ISOLEUCINE DEGRADATION
KEGG PROTEASOME
KEGG LEUKOCYTE TRANSENDOTHELIAL MIGRATION
KEGG REGULATION OF ACTIN CYTOSKELETON
KEGG TIGHT JUNCTION
KEGG LYSOSOME
KEGG PATHOGENIC ESCHERICHIA COLI INFECTION
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