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Proteomic Analysis of Laser-Captured Tubules Reveals Shared Molecular Mechanisms of Renal Tubular Damage in Immune-Related Chronic Kidney Diseases

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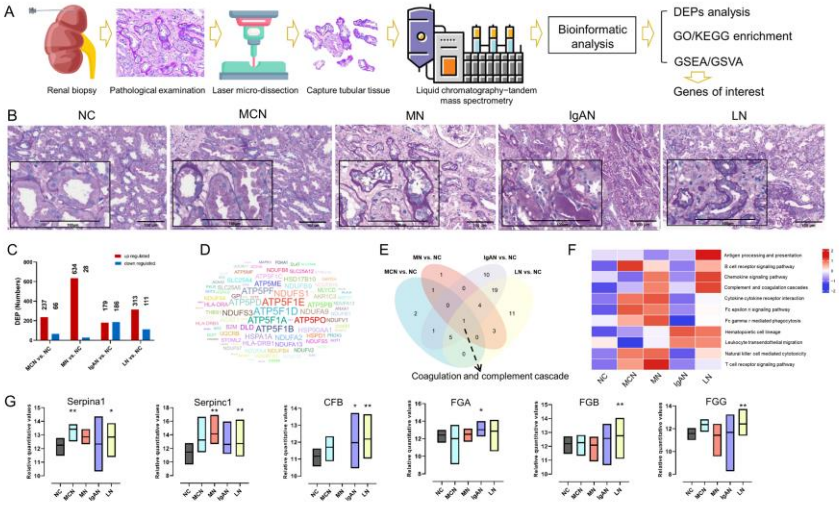
Objectives : Chronic kidney diseases including minimal change nephropathy (MCN), membranous nephropathy (MN), IgA nephropathy (IgAN), and lupus nephropathy (LN) are associated with a disrupted complement system. Despite this, the correlation between the complement system and renal tubular damage in immune-related nephropathies is not thoroughly explored. Our study focuses on investigating potential molecular mechanisms driving renal tubular damage in such diseases due to complement system imbalance.
Methods : Paraffin-embedded renal tissues from 0-point punctures of transplanted kidneys (n=10, control), MCN (n=5), MN (n=4), IgAN (n=17), and LN (n=21) were examined. Laser microdissection was used to isolate renal tubular tissue from each sample, followed by liquid chromatography-mass spectrometry-based proteomic analysis. Relative to controlsand subjects, a number of differentially expressed proteins (DEPs) were identified to functional enrichment and gene set variation/enrichment analyses.
Results : Certain commonly activated biological functions and signalling pathways were identified via GO and KEGG enrichment analyses across all the disease conditions. Quickly noticeable were those genes encoding ATP synthase F1 subunits and the pathways related to coagulation and complement cascade showing an overall increase, especially in LN.
Conclusions : In essence, abnormalities in coagulation complement cascade signalling were observed in the renal tubular tissue of all four immune-related chronic kidney diseases. These abnormalities might indirectly regulate ATP synthase F1 subunit expression, thereby negatively affecting renal tubular function. Preliminary protein-protein interaction analysis suggests that an imbalance in coagulation complement cascades possibly leads to mitochondrial damage in tubular tissues, implicating a functional disruption in tubular reabsorption. Additional studies are necessary to support these findings and elucidate the interaction details.

Figure1.png



A. Flowchart depicting the proteomic analysis of renal tubules isolated by laser capture microdissection.
B. PAS staining illustrates the renal tubules of normal controls, minimal change nephropathy, membranous nephropathy, IgA nephropathy, and lupus nephropathy, respectively.
C. Bar plots showing differentially expressed proteins in renal tubules across various immune-related kidney diseases identified by proteomics, with comparison to normal controls (NC) for up and down regulation.
D. The differentially expressed proteins in each kidney disease were subjected to GO and KEGG analysis compared with NC. The genes involved in common biological functions or signaling pathways across the five disorders were summarized, ranked by frequency, and depicted in a word cloud representing the top 100. Notably, genes encoding five subunits of mitochondrial ATP synthase were frequently involved in tubular function regulation, suggesting a shared mechanism of tubular damage in these immune-related kidney diseases.
E. A Venn diagram revealed "coagulation and complement cascade" as a shared signaling pathway markedly upregulated across different immune-related kidney diseases, as determined by GSEA analysis.
F. GSVA analysis indicated variations in expression of immune-related signaling pathways among unique immune-related kidney diseases.
G. Comparative protein expression profiles within the "coagulation and complement cascade" pathway indicated a trend towards upregulation in immune-related kidney diseases, with most notable elevation in Lupus Nephropathy (LN).
Note: NC refers to normal controls; MCN, minimal change nephropathy; MN, membranous nephropathy; IgAN, IgA nephropathy; LN, lupus nephropathy.