AEBP1 is Upregulated in Diabetic Nephropathy Biopsies

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Background: Worldwide, one in eleven adults have diabetes mellitus and 30% to 40% will develop diabetic kidney disease (DKD). A mechanistic understanding of DKD is crucial to develop treatment strategies. To unravel DKD's pathogenesis, single cell (scRNA) sequencing has proven a powerful tool, but is limited by a lack of localization. Spatial transcriptomics allows the mapping of scRNA sequencing data back to histology.

Methods: Frozen human nephrectomy and biopsy samples were processed according to Visium spatial gene expression protocols, stained with H&E, and imaged. Samples were permeabilized for RNA capture, reverse transcribed and sequenced on an Illumina NovaSeq 6000. Mapping and counting were completed in Space Ranger and data was processed in Seurat. Samples were laser microdissected, protein was isolated, and protein was quantified by HPLC-MS.

Results: Clusters from scRNAseq were mapped upon reference and DKD spatial transcriptomic images (N=4 reference, 2 DKD). Differentially expressed genes were identified in diabetic kidneys, including the upregulation of Adipocyte Enhancer Binding Protein (*AEBP1*). Pathway analysis revealed enrichment of extracellular matrix organization and immune process pathways. To increase the confidence of these findings, glomeruli and the tubulointerstitium were laser microdissected (N=7 diseased, 4 reference) for proteomic analysis. AEBP1 was upregulated in the tubular interstitium of diseased kidneys and selectively upregulated in the glomeruli of Diabetic Nephropathy samples (N=2). AEBP1 localized to the interstitium by spatial transcriptomics and was expressed in highly fibrotic regions. Glomerular expression was not observed due to glomerulosclerosis.

Conclusion: AEBP1 upregulation is a marker of interstitial fibrosis, with specific expression in the glomeruli of diabetic nephropathy specimens with glomerulosclerosis.

Impact: This is the first study utilizing spatial transcriptomics to define and localize markers of human kidney disease. Confirmatory studies are required in larger sample sizes. AEBP1 is a previously unidentified marker of DKD previously associated with fibrosis in other organ-specific diseases.